Functional Specialization in the Brain:

The Case of Numbers

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To my mum…

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Abstract

Humans as well as other animals are endowed with the capacity to extract the numerosity (i.e., the number of items) of a given set of objects. This capacity is thought to form the basis of human specific symbolic mathematical abilities. Hence, understanding its nature is of importance. One of the most influential models (The Triple Code Model) suggests that this evolutionarily ancient mechanism resides on the horizontal aspect of the intraparietal sulcus and represents number semantics in a format and modality independent fashion (i.e., magnitude code). In addition, subtraction is thought to rely more on this mechanism whereas multiplication relies more on phonological circuits (i.e., verbal code). Although there is evidence from non-human primate electrophysiology suggesting a certain degree of abstraction for number semantics in the parietal cortex, this was only found for small numerosities (<5) so far. Furthermore, in humans, the neural correlates of numerosities presented in different formats and modalities is still missing. Hence, in this thesis, we investigated how numerosities presented in different modalities (visual and auditory) and formats (simultaneous and sequential) are represented in humans using pattern recognition methods on functional magnetic resonance data. Our results indicated that the parietal magnitude system proposed by the Triple Code Model is involved only when the numerosity is presented simultaneously. Furthermore, using a dual task design, we showed that both subtraction and multiplication interact with the magnitude and verbal codes. Hence, our results call for an update on the Triple Code Model and suggest that functional specialization for numbers does not happen on a semantic level but rather has a format dependent nature.

Keywords: fMRI, multivariate pattern analysis, Triple Code Model, numerosity

Zusammenfassung

Menschen teilen mit vielen Spezies die Fähigkeit, aus einer Menge von Objekten deren Numerosität zu extrahieren. Es wird angenommen, dass diese Fähigkeit die Grundlage für die Menschen eigene, symbolisch-mathematische Fertigkeiten bildet. Daher ist ein besseres Verständnis der neuralen Charakteristiken dieser Fähigkeit von großer Bedeutung. Eines der einflussreichsten Modelle (das Triple Code Modell-TCM) nimmt an, dass dieser evolutionär alte Mechanismus in horizontalen Anteil des intraparietalen Sulcus verortet werden kann, der die Bedeutung von Anzahl in einer format- und modalitätsunabhängigen Art und Weise repräsentiert (d.h., Größencode). Zusätzlich wird angenommen, dass Subtraktion auf eben dieser Fähigkeit aufbaut, wohingegen Multiplikation stärker auf phonologischen Verarbeitungsmechanismen beruht (d.h., verbaler Code). Elektrophysiologische Untersuchungen beim Affen deuten auf einen gewissen Grad an Abstraktion von semantischer Größeninformation im parietalen Kortex hin. Jedoch wurde dies bisher nur für kleine Numerositäten (<5) berichtet. Außerdem konnte das neurale Korrelat für Numerositäten in unterschiedlichen Formaten und Modalitäten bisher nicht lokalisiert werden. Deshalb haben wir in dieser Arbeit untersucht, wie Numerositäten beim Menschen repräsentiert werden, wenn diese in verschiedenen Modalitäten (visuell und auditorisch) und Formaten (simultan und sequenziell) präsentiert werden. Die erhobenen funktionellen Magnetresonanztomografiedaten wurden mittels maschineller Lernalgorithmen analysiert. Unsere Ergebnisse legen nahe, dass das vom TCM postulierte parietale Größensystem nur dann involviert ist, wenn die Numerositäten simultan präsentiert werden. Zusätzlich konnten wir zeigen, dass sowohl Subtraktion als auch Multiplikation auf Größen- sowie verbale Codes- zurückgreifen. Unsere Befunde unterstreichen daher die Notwendigkeit einer Aktualisierung des TCMs und legen nahe, dass die funktionelle Spezialisierung für Mengen formatabhängig ist.

Stichworte: fMRI, Support-Vector-Maschinen, Triple Code Modell, numerosität

Table of Contents

1. Introduction **1**

2 Neural Basis of Arithmetic Operations **6**

2.1 Lesion studies *6*

2.2 Behavioral studies *7*

2.3 fMRI studies *9*

3 Neural Basis of Abstract Magnitude Code **12**

3.1 Electrophysiology studies *12*

3.2 fMRI studies *15*

3.3 The gap between electrophysiology and fMRI *17*

4 Open Questions **20**

4.1 Can factors beyond operation type account for the claimed dissociation between subtraction and multiplication? *20*

4.2 Representation of numerical information presented over time and across sensory modalities *21*

4.3 How is numerosity extracted and how is it related to other magnitudes? *22*

5 Summary of Empirical Studies **25**

5.1 Study 1 ..... *25*

5.2 Study 2 ..... *28*

5.3 Study 3 ..... *31*

6 Conclusions **36**

6.1 Implications for the Triple Code Model *37*

6.2 Implications for functional specialization in the brain *39*

7 Future Directions **42**

8 Abbreviations **44**

9 References **45**

10 Included Manuscripts **53**

11 Manuscript 1 ..... **54**

12 Manuscript 2 ..... **55**

13 Manuscript 3 ..... **56**

The aim of science is not to open the door to infinite wisdom, but to set a limit to infinite error.

-Bertolt Brecht

1 Introduction

Unraveling the basic principle underlying brain's functional organization has been a great challenge for neuroscientists for centuries. One of the most prominent ideas in this regard was introduced by the Viennese physician Franz Joseph Gall (1758-1828). According to Gall, the brain is a modularized organ that controls behavior and has a specialized region for each personality trade. Although we know today that his ideas were far from truth, one argument that he introduced, the functional specialization in the brain (aka modularity), is still debated.

One of the first experimental studies on modularity in the brain was conducted by the French physician Pierre Paul Broca (1824-1880). He discovered that patients who had aphasia suffered from lesions in the left frontal region (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007). This was taken as the first anatomical evidence of functional specialization for language in the brain. Later on, with the advancement of imaging and electrophysiological methods, other high level cognitive functions like object recognition, motion, face and body perception were studied and suggested to have dedicated and localized brain circuitries as well (see Kanwisher, 2010 for a review). Hence, most neuroscientists would agree today that there is accumulating evidence in favor of at least a certain degree of specialization in the brain. Still, some important questions remain to be answered.

First, when the brain is observed on a network level using imaging techniques, even regions that are thought to be specialized for one function are, in some cases, activated for other functions as well (e.g., Broca's area is activated when participants see hand actions without any language content; Fadiga & Craighero, 2000; Fadiga et al., 2006). Second, while

functional specialization is more clearly exhibited for sensory processes like vision and audition, it is improbable to have a specialized unit for each high level process. In an evolutionary perspective, it is unlikely that selective pressures took place in such a short time that could lead to the biological changes required for specialization for recent cultural inventions like reading and arithmetic. To account for this gap, Dehaene & Cohen (2007) proposed the 'Neuronal Recycling' hypothesis that explains how recent developments like mathematics and reading might have emerged without selective evolutionary pressures.

According to the idea of neuronal recycling, new cultural inventions are built on evolutionarily old circuits with the help of neuronal plasticity. Following this, human inventions like reading and mathematics should share neural circuits with evolutionarily older functions. For the case of mathematics, one possible candidate was suggested to be the visuospatial working memory and attention circuits in the parietal cortex, as these areas have repeatedly been shown to be involved in mental arithmetic (Dehaene & Cohen, 2007).

In accord with the predictions of neuronal recycling, primate electrophysiology studies reported neurons in the superior parietal lobule (SPL) coding for the number of arm movements executed (Sawamura, Shima, & Tanji, 2002) as well as neurons in the lateral prefrontal (Nieder, Freedman, & Miller, 2002) and parietal cortex (Nieder, Diester, & Tudusciuc, 2006) coding for the number of visual items presented. As natural as it seems to think of numbers as a unique human invention dependent on language, these studies suggested that even functions which we think of as very human and high level can be ontogenetically ancient and modular in the brain.

The above mentioned electrophysiological findings were also taken to support an early influential model of numerical cognition, that is the Triple Code Model (TCM) (Dehaene & Cohen, 1995; Dehaene, Piazza, Pinel, & Cohen, 2003; Renzi, 1997). Still being the leading

model in the field, the TCM postulates three interacting yet distinct neural codes for numerical cognition (Figure 1). The *Arabic number code* is used for multi-digit arithmetic operations. It resembles the visual word form representation in the sense that it processes the visual properties of the number symbols but not the semantic or phonological content. It is associated with the activity in bilateral fusiform and lingual regions during processing of visually presented Arabic digits. The *verbal number code* is used for performing phonologically coded arithmetic operations like single-digit multiplication and addition. It stores arithmetical facts in a phonological form. It is associated with activity in the left-hemisphere perisylvian language areas and the left angular gyrus (AG). The *abstract magnitude code* is used for language independent magnitude understanding. In contrast to Arabic and verbal number codes, it represent the semantic content of numerical information independent from visual and phonological properties. It is associated with activity in the horizontal aspect of the intraparietal sulcus (hIPS), partially in line with electrophysiological findings (Nieder & Dehaene, 2009).

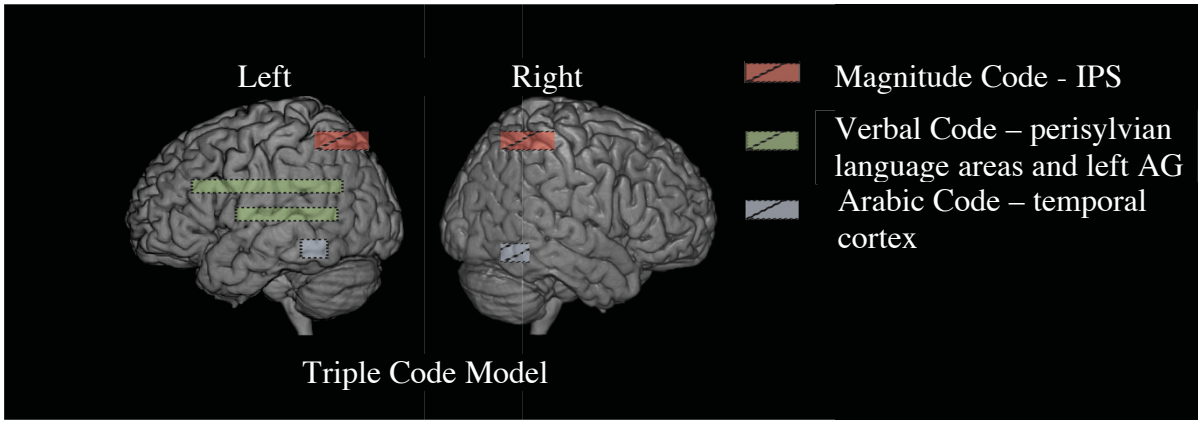

Figure 1. Schema of the Triple Code Model. *Magnitude code* (red) resides in bilateral intraparietal sulcus (IPS). It is thought to be an innate, non-verbal mechanism that represents numerosities in a format and modality independent fashion. *Verbal code* (green) resides on left hemispheric language areas and angular gyrus. It stores memorized arithmetic facts like multiplication tables or simple additions. *Arabic code* (blue) resides on bilateral temporal cortex. It represents number symbols (e.g., '5') and is involved in symbolic arithmetic.

While the involvement of language areas and the temporal cortex in mental arithmetic is widely accepted in the field, the abstract magnitude code postulation of the TCM is still highly debated. First, the parietal cortex is involved in many other functions in humans from action planning to attention (Colby & Goldberg, 1999). Therefore, it was thought to be a general processor rather than having specialization for certain functions. Second, the nature of the abstract magnitude code is still being debated. The TCM denotes the abstract magnitude code as an innate system enabling us to comprehend and represent magnitudes in a language (e.g., Arabic digits vs. an array of objects), presentation format (e.g., array of object presented over time vs. over space) and modality (e.g., visual or auditory) independent manner. Yet, contradictory evidence has been collected on this account (see Cohen Kadosh & Walsh, 2009 for a discussion).

In addition, the TCM predicates dissociation for certain types of arithmetic operations. That is, subtraction is thought to rely more on the abstract magnitude code while addition and multiplication rely more on the verbal number code (Dehaene, Molko, Cohen, & Wilson, 2004). Yet, recent studies reported inconsistent results regarding the claimed dissociations (DeStefano & LeFevre, 2004; Fürst & Hitch, 2000; Lee & Kang, 2002; Logie, Gilhooly, & Wynn, 1994; Seitz & Schumann-Hengsteler, 2000; Seyler, Kirk, & Ashcraft, 2003).

The present thesis will investigate the postulations of the TCM in the context of functional specialization in the brain. Specifically, the claimed dissociation between different arithmetic operation types and modality and format independence of the magnitude representation will be investigated using behavioral measures and functional magnetic resonance imaging (fMRI). In the following chapter (Chapter 2) a summary of lesion, behavioral and fMRI studies regarding the claimed dissociation between different arithmetic operation types will be given. Chapter 3 will introduce the data from primate electrophysiology as well as human imaging studies dealing with the nature of the abstract

magnitude representation. Chapter 4 will delineate the open questions that remain to be answered in the field of numerical cognition. Chapter 5 will provide a summary of the empirical studies conducted within the scope of this thesis. The significance of these studies for the TCM and functional specialization in the brain in general will be discussed in Chapter 6. Finally, directions for future research will be given in Chapter 7.

2 Neural Basis of Arithmetic Operations

One of the central claims of the TCM is the dissociation of neural pathways employed for different types of arithmetic operations. In the TCM, multiplication and addition depend more on arithmetic fact retrieval and hence recruit the articulatory loop (i.e., verbal code) while subtraction depends more on quantity manipulation and hence recruit the parietal cortex (i.e., abstract magnitude code). While some initial case studies with lesion patients seemed to support these postulations, recent studies suggest that observed dissociations could be due to factors like educational or cultural differences (Imbo & LeFevre, 2010) or individual strategy selection bias (Imbo & LeFevre, 2010) rather than the specific arithmetic operation type per se. Relevant studies will be presented in following sections.

2.1 Lesion studies

One of the first suggestions for a neural dissociation between different arithmetic operations came from a lesion study with two acalculic patients (Dehaene & Cohen, 1997), patient MAR who had right inferior parietal lesion, and patient BOO who had a left subcortical lesion. Interestingly, although both patients suffered from pure anarithmetia (i.e., while reading and writing of Arabic digits were fully intact, pronounced deficits in calculation were observed), a detailed investigation revealed that patient MAR had more difficulties in performing subtractions whereas patient BOO had more difficulties in multiplications. This finding was interpreted as an evidence for a dissociation between arithmetical fact retrieval (employed more strongly during multiplication) and manipulation of numerical quantities (employed more strongly during subtraction).

Dehaene & Cohen's (1997) finding was later supported by Lee (2000). Lee (2000) reported a patient with hemorrhage around the left parieto-temporal junction and an accompanying deficit in multiplication but not in subtraction. Moreover, another case with two acalculic patients with selective deficits for subtraction and multiplication was reported (Lemer, Dehaene, Spelke, & Cohen, 2003). One patient had a left parietal lesion and an accompanying deficit in subtraction while the other had semantic dementia due to left temporal hypometabolism with an accompanying deficit in multiplication (Lemer et al., 2003).

On the other hand, another case study with three patients reported selective deficits for addition, multiplication and subtraction (van Harskamp & Cipolotti, 2001). This result is contradicting previous claims since, according to the TCM, both addition and multiplication rely on the verbal code. Hence, once there is a deficit in verbal code areas, both addition and multiplication should be impaired. The possibility of having deficits in addition with intact multiplication suggests a more complicated story than what was originally postulated.

2.2 Behavioral studies

One of the most prominent models of working memory proposed by Baddeley predicates four working memory components: visuospatial sketchpad, phonological loop, episodic buffer and central executive (Baddeley & Hitch, 1974; Baddeley, 2000; Figure 2). The visuospatial sketchpad and phonological loop are thought to store visuospatial and phonological information, respectively, for a short time, whereas the episodic buffer combines phonological and visuospatial information over time and serves as a gateway to long term memory. The central executive, on the other hand, is a control mechanism that orchestrates the three slave systems (i.e., visuospatial sketchpad, phonological loop and episodic buffer).

The verbal code postulated in the TCM resides on the same neural structures as the phonological loop, and the abstract magnitude code resides on the same neural structures as the visuospatial sketchpad of Baddeley's model of working memory (DeStefano & LeFevre, 2004; Logie et al., 1994; Zago & Tzourio-Mazoyer, 2002). Following this logic, a group of behavioral studies were conducted after the dissociations observed in lesion studies (Chapter 2.1). Lee & Kang (2002) reported a double dissociation between addition and phonological working memory vs. subtraction and visuospatial working memory. In contrast, other behavioral studies investigating mental calculation and working memory interaction failed to find the claimed dissociation or reported contradictory results.

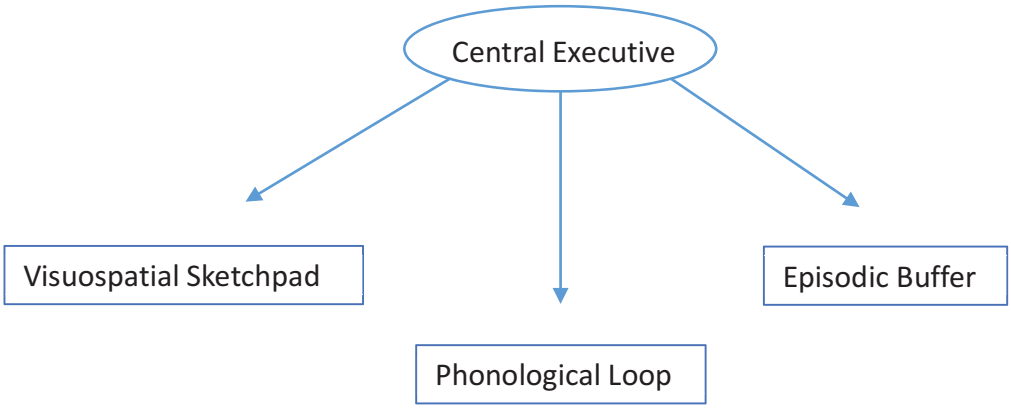

Figure 2. Baddeley's model of working memory. The Central Executive is a system that controls and orchestrates the three slave systems: Visuospatial sketchpad, phonological loop and episodic buffer. Visuospatial sketchpad stores visuospatial information, phonological loop stores verbal information and the episodic buffer combines these two types of information and communicates with long term memory to form episodic memory.

To begin with, Seitz & Schumann-Hengsteler (2000) used an articulatory suppression task while participants were solving simple and complex multiplications. Only complex multiplications were impaired in the presence of articulatory suppression. In contrast, De

Rammelaere, Stuyven, & Vandierendonck (2001) found no effect of articulatory suppression on the verification of correct multiplications. Seyler, Kirk, & Ashcraft (2003) showed that a secondary letter span task decreased the performance in both simple and complex subtraction problems. Imbo & LeFevre (2010) demonstrated an interaction between visuospatial working memory and multiplication and between phonological working memory and subtraction. Taken together, these studies speak against a full degree of double dissociation between different arithmetic operations (subtraction and multiplication) and working memory pathways (visuospatial and phonological).

One of the reasons why the above mentioned behavioral studies reported contradicting results could be related to the fact that they employed different visuospatial and phonological working memory tasks and different levels of difficulty both for calculations and for working memory tasks. This might have affected the degree of interaction between different working memory pathways and arithmetical operations.

2.3 fMRI studies

Following reports of dissociation between different arithmetic operations in lesion and behavioral studies, the neural basis of mental arithmetic in healthy participants was investigated extensively with fMRI. While initial studies provided neural evidence supporting the dissociation between subtraction and multiplication, results from more recent studies contradict with at least a full degree of dissociation between different arithmetic operations.

Lee (2000) reported differential activation for simple subtraction and multiplication problems in an fMRI task. Multiplication induced greater blood-oxygen-level dependent

(BOLD) signal in the left AG, supramarginal gyrus and superior frontal gyrus compared to subtraction, whereas subtraction induced greater BOLD signal in bilateral intraparietal sulcus (IPS), superior and inferior frontal gyri and posterior inferior temporal gyri compared to multiplication. Ischebeck et al. (2006) trained participants in mental subtraction and multiplication tasks. Training had different influence on neural level for subtraction and multiplication. While both operations exhibited a decrease in BOLD signal in inferior frontal and parietal regions, there was an additional increase in BOLD signal in AG for multiplication, but not for subtraction. Finally, when the neural basis for complex versus simple calculations was investigated for all operation types (i.e., subtraction, addition, multiplication and division), only the medial and superior frontal gyrus showed an increase in BOLD signal for all operations and the parietal BOLD increase was observed for all operations but multiplication (Fehr, Code, & Herrmann, 2007). Taken together, these results are in line with the prediction of the TCM that multiplication relies more on the verbal code whereas subtraction relies more on the magnitude code, as they all point to a greater involvement of inferior and superior parietal cortices in subtraction and a greater involvement of AG in multiplication.

In contrast, an fMRI guided transcranial magnetic stimulation on the hIPS decreased the performance of participants both in mental subtraction and multiplication tasks providing causal evidence for an involvement of hIPS in multiplication as well (Andres, Pelgrims, Michaux, Olivier, & Pesenti, 2011). Rosenberg-Lee, Chang, Young, Wu, & Menon (2011) studied the neural basis of all arithmetic operations using cytoarchitechtonically defined region of interests (ROI) and failed to find a difference between subtraction and multiplication in the left IPS and AG. Moreover, they reported a high degree of individual variability in neural basis of different arithmetic operations. Taken together, these studies contradict a full degree of dissociation between subtraction and multiplication. Rather, they indicate that the

parietal cortex can also be involved in multiplication and the AG can also be involved in subtraction depending on task demands and participants.

Although it might look difficult to reconcile the above mentioned results, it should be noted that the quoted studies varied substantially with respect to the level of difficulty for arithmetic operations and baseline. Furthermore, none of the studies so far checked the interaction between arithmetic operations and working memory pathways in a reciprocal fashion (i.e., how working memory tasks are affected by a concurrent calculation, as well as how calculations are affected by a concurrent working memory task). Considering the fact that there is a high degree of individual variability for different arithmetic operations (Rosenberg-Lee et al., 2011), individual skill levels might also have affected the degree each participant relied on a specific route (Demir, Prado, & Booth, 2014). In line with this, a recent fMRI study reported that observed neural differences between different arithmetic operations disappear when one asks participants the strategies they used to solve the arithmetic problems and controls for these (Tschentscher & Hauk, 2014).

To summarize, evidence from recent fMRI studies converge on the idea that the observed dissociations between different arithmetic operations are due to factors like individual strategy selection and experienced difficulty rather than a core difference between different arithmetic operations.

3 Neural Basis of Abstract Magnitude Code

According to the TCM, the IPS entails an evolutionarily ancient and abstract quantity system. That is, the Arabic number '3', number word 'three', or an array of three objects ('♥ ♥ ♥') presented at the same time (simultaneously) or over time (sequentially) would all be mapped onto the quantity system in IPS (see Figure 3 for a depiction of possible ways of presenting numerosity information). Although the involvement of IPS in mental calculation was repeatedly shown, the nature of the abstract magnitude code is still under debate, as it postulates a semantic role for IPS beyond its involvement in calculation related manipulation of numerical information (Dehaene, Piazza, Pinel, & Cohen, 2003). In the following sections, relevant electrophysiology and fMRI studies as well as the gap between these two will be discussed.

3.1 Electrophysiology studies

The first evidence for parietal number coding came from a primate electrophysiology study (Sawamura et al., 2002). Sawamura et al. (2002) reported neurons in the SPL of two trained monkeys that were tuned to the number of arm movements executed. Following this, labeled line coding for the number of simultaneously presented visual items in monkey prefrontal (Nieder et al., 2002) and parietal cortex (Nieder & Miller, 2004) as well as corvid songbird endbrain (Ditz & Nieder, 2015) was reported. Interestingly, the spiking activity was observed 30-60ms earlier in the parietal cortex compared to the prefrontal cortex (Nieder & Miller, 2004), suggesting that the information flows from the parietal to the prefrontal cortex.

Furthermore, numerosity selectivity in parietal and prefrontal cortices exists even before training (Viswanathan & Nieder, 2013), indicating that the extraction of numerosity

depends on an innate mechanism. Training increases the numerosity-specificity of prefrontal neurons but not parietal (Viswanathan & Nieder, 2015), pointing towards a more executive role for the prefrontal cortex and a numerosity-specific role for the parietal cortex.

The labeled line coding for the number of simultaneously presented visual items exists for small (1-5) as well as for large numerosities (>5) in the prefrontal cortex, with a decreasing degree of specificity as numerosity increases (Nieder & Merten, 2007). Yet, only monotonically coding neurons are reported till now for large simultaneous numerosities in primate parietal cortex (Roitman, Brannon, & Platt, 2007). On the other hand, neurons tuned to the number of items presented over time (i.e., sequential) was found only for small numerosities so far (Nieder et al., 2006). Interestingly, some of these neurons are tuned to the number of sequentially presented items independent of modality (i.e., visual objects or auditory beeps; Nieder, 2012). However, supramodal neurons constitute a small proportion of numerosity-selective neurons in the parietal cortex, as most of numerosity-selective neurons respond only for one modality (Nieder, 2012).

A recent study on human patients with cortical implants reported that the same set of neurons in the IPS respond when patients are engaged in symbolic calculation tasks and when they refer to the numerical contents of objects in real life (Dastjerdi, Ozker, Foster, Rangarajan, & Parvizi, 2013). Although this study is not directly related to the representation of abstract magnitude, it provides a very strong neurophysiological support for a certain degree of functional specialization in human IPS for symbolic numerical concepts. However, as only symbolic numbers were investigated in this study, the neurophysiology of non-symbolic magnitude representation in humans is still to be resolved. In contrast to humans, the prefrontal cortex plays a more central role in monkeys compared to the IPS in connecting Arabic number symbols to corresponding non-symbolic numerosities (Diester & Nieder, 2007).

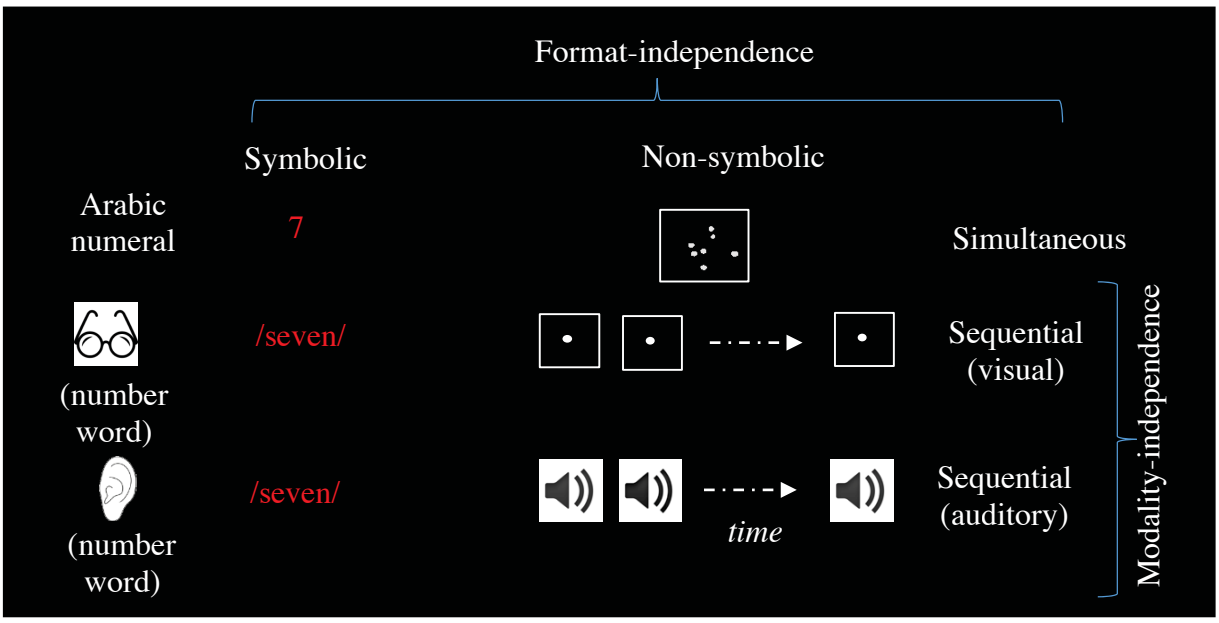

Figure 3. Schema depicts possible ways of presenting numerical information. Left column (symbolic): Language based presentation of numbers. Numerical information is presented using numerals (e.g., Arabic numeral 7 or Roman numeral VII) or written/spoken number words (e.g., 'seven'). Right column (non-symbolic): Language-independent presentation. A set of objects are presented either over space (simultaneous) or over time (sequential). The idea that number semantics is represented in the same circuitry independent of whether it was presented as Arabic numeral, number word or set of objects in simultaneous or sequential format will be referred to as *format-independence*. The idea that number semantics is represented in the same circuitry independent of whether it was presented in visual, auditory or another modality will be referred to as *modality-independence*.

To summarize, there is electrophysiological evidence supporting numerical specialization of some neurons in the parietal cortex, especially in the IPS. Furthermore, there are neurons in primate parietal cortex that represent the semantic meaning of numerosity independent of presentation format (i.e., simultaneous or sequential) and modality (i.e., visual or auditory) for small numbers. Yet, whether labeled line coding as well as format and modality independence for large numerosities exists in the parietal cortex is still to be resolved, which is an essential test for the claimed numerical specialization of IPS.

3.2 fMRI studies

Although electrophysiology studies suggest at least a certain degree of abstract magnitude coding in the parietal cortex, it is not trivial to assess whether non-symbolic numerosity coding in monkeys would generalize to symbolic numbers as well. This is an essential test for the abstract magnitude code as it is thought to provide the evolutionary basis for symbolic mathematics (Dehaene & Cohen, 2007; Halberda, Mazzocco, & Feigenson, 2008). The only electrophysiology study on symbolic number learning in monkeys reported a greater involvement of the prefrontal cortex rather than IPS in connecting Arabic number symbols to non-symbolic numerosities (Diester & Nieder, 2007). Human imaging studies conducted over the last decades to resolve the nature of numerosity coding in the parietal cortex have been controversial.

To begin with, tasks that involve manipulation or comparison of numerosities activate common regions in the parietal cortex for Arabic numerals and simultaneous numerosities (He, Zuo, Chen, & Humphreys, 2014; Holloway, Price, & Ansari, 2010) and for auditory and visual sequential numerosities (Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003). Although these were interpreted to support format and modality-independence, respectively, common activation does not necessarily mean common representation for number-semantics. In line with this, other studies showed that when response and difficulty related factors are eliminated, the involvement of IPS in these tasks disappears (Göbel, Johansen-Berg, Behrens, & Rushworth, 2004; Shuman & Kanwisher, 2004). Hence, to overcome task related confounds, fMRI pattern recognition and adaptation were used to investigate format and modality independence of numerosity representations.

Multivariate pattern recognition analysis (MVPA) revealed a distributed representation of non-symbolic simultaneous numerosity in the parietal cortex (Bulthé, De

Smedt, & Op de Beeck, 2014; Dormal, Andres, Dormal, & Pesenti, 2010; Eger et al., 2009; Eger, Pinel, Dehaene, & Kleinschmidt, 2013; Lyons, Ansari, & Beilock, 2015). Yet, generalization from non-symbolic simultaneous numerosities to symbolic numerosities (and vice versa) was not successful, contradicting the idea of format-independence (Bulthé et al., 2014; Dormal et al., 2010; Lyons et al., 2015).

Adaptation studies using passive viewing of number words ('two') and Arabic numerals ('2') (Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007; Naccache & Dehaene, 2001) or non-symbolic simultaneous numerosities and Arabic numerals (Demeyere, Rotshtein, & Humphreys, 2014; Piazza, Pinel, Le Bihan, & Dehaene, 2007) revealed neural adaptation for quantities in IPS. However, these studies reported different hemispheric lateralization for quantity adaptation and generalization of adaptation across presentation formats. While Piazza et al. (2007) reported neural adaptation for non-symbolic simultaneous numerosities and Arabic numerals in both hemispheres, Cohen Kadosh et al. (2007) reported that neural adaptation for number words and Arabic numerals existed only in the left hemisphere. Moreover, the adaptation was generalized between formats only in the right hemisphere in the Piazza et al. (2007) study and only in the left hemisphere in the Cohen Kadosh et al. (2007) study, limiting the interpretability of these results in terms of format-independent representation of number semantics.

A recent study using high field (7T) fMRI revealed topographic mapping in the parietal cortex for non-symbolic simultaneous numerosities but not for Arabic numerals (Harvey, Klein, Petridou, & Dumoulin, 2013). In addition, parietal topographic mapping of non-symbolic numerosities and object-size are intermingled (Harvey, Fracasso, Petridou, & Dumoulin, 2015). Finally, the parietal cortex contains object related information as well along with numerosity (Silver & Kastner, 2009). In line with this, Bulthé, De Smedt, & Op de Beeck (2015) showed that the pattern of activation for Arabic numerals resemble most the

pattern of activation for one object (i.e., '7' activates a pattern that resembles most the pattern of one dot instead of seven dots). This suggests that the numerosity representation in the parietal cortex might be limited to the representation of number of objects rather than a domain-specific abstract number system.

While most human imaging studies focused on Arabic numerals or non-symbolic simultaneous numerosities, primate electrophysiology studies suggest that there are neurons in the parietal cortex tuned to small sequential numerosities as well (Nieder et al., 2006). In accordance with this, a recent fMRI study reported adaptation to small sequential auditory numerosities in IPS (habituation numerosity four, deviants two and six; Wang, Uhrig, Jarraya, & Dehaene, 2015). Yet, the idea of an abstract number system foresees representation of large sequential numerosities in the parietal cortex as well. There is so far no electrophysiological or imaging evidence that large sequential numerosities are also represented in the parietal cortex in the absence of task/response related signals.

In sum, there is a distributed representation of non-symbolic simultaneous numerosities in the parietal cortex as it was repeatedly demonstrated by MVPA studies (Bulthé et al., 2014, 2015; Dormal et al., 2010; Eger et al., 2009, 2013; Lyons et al., 2015). Yet, converging evidence suggests that either a format and modality independent abstract magnitude code for numerosities does not exist or it is represented in a spatial scale that is not possible to capture with conventional non-invasive imaging methods.

3.3 The gap between electrophysiology and fMRI

As mentioned above (Chapter 3.1), primate electrophysiology studies reported numerosity tuned neurons in prefrontal and parietal cortices (Nieder et al., 2002; Nieder &

Miller, 2004). A small proportion of these neurons are tuned to numerosity independent of presentation format (i.e., simultaneous vs .sequential; Nieder et al., 2006) and modality (i.e., visual vs. auditory; Nieder, 2012). In contrast, fMRI pattern recognition studies on Arabic numerals and simultaneous numerosities failed to find a common representation (Bulthé et al., 2014, 2015; Eger et al., 2013; see Eger et al., 2009 for another view). Although this might seem controversial, the data from electrophysiology and fMRI studies should be combined with caution.

First of all, it should be noted that modality and format independent numerosity coding in primate parietal cortex was found only for small numerosities (Nieder et al., 2006; Nieder, 2012). Yet, in a domain specific abstract number system large numerosities (>5) should also be represented. While distributed representation for large simultaneous numerosities was reported by fMRI pattern recognition studies (Eger et al., 2009, 2013), single-cell electrophysiology reported only monotonic coding for large simultaneous numerosities in the parietal cortex so far (Roitman et al., 2007) and no electrophysiological evidence was yet collected regarding the coding of large sequential numerosities in the parietal cortex. Considering these, we lack evidence for an abstract coding of large magnitudes (>5) even in the electrophysiology domain.

Furthermore, while electrophysiology studies measure single-cell spiking activity, even a single voxel in fMRI data contains millions of neurons (Logothetis, 2008). fMRI BOLD signal correlates better with local field potentials (LFP) that are the summed electrical current flowing through neurons within a small volume of neural tissue (Goense & Logothetis, 2008). fMRI pattern recognition methods report a distributed representation of information mostly over a scale of hundreds of voxels (hundreds of millions of neurons, see Figure 4 for a depiction of scales used in neuroscience). This is very different from single-unit measures obtained from electrophysiology studies both in terms of spatial scale (single

neurons vs. millions), the type of neural activity (spiking activity vs. LFP) and representation (single neuron tuning vs. distributed representation over patterns of activation). In addition, a weak clustering of tuned neurons can result in negative findings in fMRI pattern recognition studies (Dubois, de Berker, & Tsao, 2015). In contrast, fMRI adaptation methods can access sub-voxel level neuronal adaptation through repeated stimulation. Yet, depending on the duration of stimulation, exhaustion of blood vessels can be mistaken for neuronal adaptation even if different neuronal populations are addressed (Krekelberg, Boynton, & van Wezel, 2006). Hence, a one-to-one correspondence between fMRI and single-unit electrophysiology remains difficult.

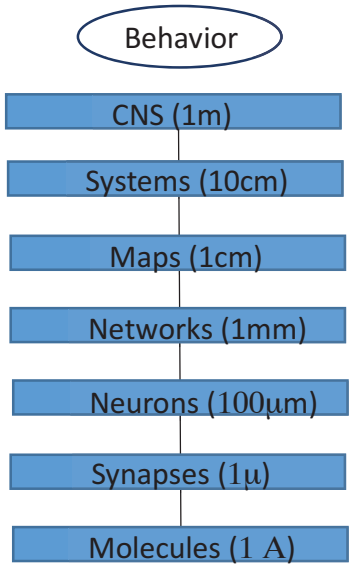

Figure 4. Depiction of different measuring scales in neuroscience. fMRI works mostly above network level (>= mm range) whereas electrophysiology works on neuronal level (μ range).

4 Open Questions

4.1 Can factors beyond operation type account for the claimed dissociation between subtraction and multiplication?

The TCM suggests that subtraction relies more on the abstract magnitude code whereas multiplication relies more on the verbal code. These codes resemble the dual system view of Baddeley's working memory architecture (Baddeley & Hitch, 1974; Baddeley, 2000). The abstract magnitude code resides adjacent to areas upon which the visuospatial sketchpad of Baddeley's model relies (e.g., IPS) whereas the verbal code resides on the same areas as the phonological loop (e.g., AG). Hence, a specific interaction between a certain memory pathway and arithmetic operation would inform us about the validity of the TCM's prediction along with the neural basis of different arithmetic operations.

While initial studies reported a dissociation between subtraction and multiplication (Dehaene & Cohen, 1997; Lee, 2000; Lemer et al., 2003) as well as a differential interaction between subtraction and visuospatial working memory vs. multiplication and phonological working memory (Lee & Kang, 2002), following behavioral, lesion and fMRI studies reported contradictory findings (S De Rammelaere et al., 2001; Imbo & LeFevre, 2010; Seitz & Schumann-Hengsteler, 2000; Seyler et al., 2003; Tschentscher & Hauk, 2014; van Harskamp & Cipolotti, 2001). Nonetheless, it should be noted that all relevant studies used diverging levels of difficulty (e.g., different levels of problem size for different operations or different spans for working memory tasks) and response modes (e.g., active production, two-alternative forced-choice or verification). This limits the interpretability of these results.

Considering the controversial results in the field, it still remains to be seen whether an operation type specific interaction exists between different working memory pathways (visuospatial and phonological) and arithmetic operations (subtraction and multiplication) or

previously observed dissociations can be attributed to factors beyond operation type. Hence, *Study 1* investigated in a reciprocal fashion how the interaction between different arithmetic operations (subtraction and multiplication) and working memory pathways (visuospatial and phonological) changes as a function of difficulty and whether the claimed dissociation between arithmetic operations holds when difficulty-related factors are controlled for.

4.2 Representation of numerical information presented over time and across sensory modalities

A small proportion of neurons in the primate parietal cortex represent numerosity independent of presentation format (i.e., simultaneous vs. sequential; Nieder et al., 2006) and modality (i.e., visual vs. auditory; Nieder, 2012). Yet, neural evidence for a format and modality-independent numerosity representation in humans is still lacking. A recent study suggests that the same visual saliency map architecture can account for both working memory and simultaneous numerosity perception capacities (Knops, Piazza, Sengupta, Eger, & Melcher, 2014). As saliency maps are part of the visuospatial attention system, it remains to be answered if the same circuitry can be employed when items are presented at the same location over time (i.e., without spatial or saliency content) and across modalities (auditory vs. visual). Thus, *Study 2* investigated the representation of visual and auditory sequential numerosities using fMRI pattern recognition within the context of a numerical comparison task.

4.3 How is numerosity extracted and how is it related to other magnitudes?

Accumulating evidence suggests that non-symbolic simultaneous numerosity is represented in the parietal cortex (Bulthé et al., 2014, 2015; Eger et al., 2009, 2013). Yet, how the brain extracts this information is still under debate. While various computational models were suggested, experimental evidence still remains inconclusive.

To begin with, Dehaene & Changeux (1993) suggested a computational model with a dedicated system for numerosity detection. In this model, the stimulus is first normalized for object size and location. Summation of activity from normalized input units yields a numerosity estimation that is later filtered by numerosity detectors. Finally, with the addition of short term working memory network, the model accounts for numerosity comparison abilities and explains well-known behavioral phenomena like Fechner's law (i.e., perceived numerosity is proportional to the logarithm of the stimulus) and distance effect (i.e., close numbers are more difficult to compare than numbers with large numerical distance).

A second model using unsupervised learning (back propagation) with a hidden layer could also account for numerosity-selective neurons found in electrophysiological studies (Verguts & Fias, 2004). After certain amount of training, the hidden layer acted as a summation unit that was numerosity sensitive (but not selective). That is, the activity in the unit increased by increasing numerosity but no tuning was observed. The summed activity from the hidden unit was then relayed to numerosity-selective units that had tuning for specific numerosities. In addition, after unsupervised learning of non-symbolic numerosities, a symbolic unit was added to the model and trained again together with the summation unit obtained from unsupervised learning of non-symbolic numerosities. The model successfully

attached number symbols to non-symbolic numerosities and could account for behavioral phenomena like distance effect.

In addition to computational models proposing a dedicated mechanism for numerosity detection, there are models developed based on visual properties of images. Morgan, Raphael, Tibber, & Dakin (2014) suggested that numerosity can be simply texture extraction. That is, the amount of contour in an image can be estimated by combined output of 'edge detectors' that are responsive to local changes in luminance. Moreover, Stoianov & Zorzi (2012) could reproduce numerosity-related behavior through unsupervised learning with a hidden generative model based on visual properties of stimuli, that is without any numerosity-related training.

Last but not least, while it is widely assumed that the representation of non-symbolic simultaneous numerosities is not affected by non-numerical sensory features (e.g., diameter, total area, density or convex hull), performance in numerosity comparison and estimation changes as a function of the congruency between numerosity and sensory features (Gebuis & Reynvoet, 2012a, 2012b; Raphael, Dillenburger, & Morgan, 2013; Raphael & Morgan, 2015). Line length coding neurons are intermingled with numerosity neurons in primate lateral intraparietal cortex (LIP; Tudusciuc & Nieder, 2007) and topographic representations of numerosity and object size are also intermingled in human parietal cortex (Harvey et al., 2015, 2013). Taken together, these led to the idea that numerosity-related signals could also be capturing a weighted average of sensory representations or the numerosity itself could be extracted from a weighted average of sensory dimensions (Gebuis, Gevers, & Cohen Kadosh, 2014).

To summarize, while it is established that there are numerosity-selective neurons in primate IPS and numerosity-related representation in human parietal cortex, we still do not

know how this information is extracted and whether this is the basis of an abstract magnitude system or not. Furthermore, while most of the research concentrated on the representation of numerosity in the parietal cortex, numerosity perception is affected by visual properties of stimuli and it can be adapted like other low level sensory features (Burr & Ross, 2008). Still, no detailed investigation on the role of visual cortex was done so far. In this regard, fMRI has an advantage over electrophysiology as it allows measuring activity from different areas in the brain at the same time, in contrast to electrophysiology that is mostly limited to recording from a single site or at most a few sites simultaneously. In addition, all the computational models mentioned above explain how numerosity is extracted in simultaneous presentation format. Hence, it still remains to be resolved if the same mechanism can account for sequential numerosities as well. On this line, *Study 3* investigated how numerosity and sensory features like dot diameter, total area, convex hull and density of non-symbolic simultaneous numerosities are represented and how they evolve from early visual areas to the parietal cortex.

5 Summary of Empirical Studies

5.1 Study 1

The TCM postulates that whereas subtraction and division depend more on the abstract magnitude code that resides on parietal visuospatial circuits, multiplication and addition depend more on the verbal code that resides on phonological circuits (Dehaene et al., 2003). Yet, only one behavioral study reported thus far a differential suppression between visuospatial working memory & subtraction and phonological working memory & multiplication (Lee & Kang, 2002). Importantly, none of the previous studies controlled for inter and intra subject difficulty of calculation problems and working memory tasks. Also, previous studies only assessed the effect of secondary working memory tasks on calculations, whereas a selective interaction between working memory pathways and operation types implies that the performance in working memory tasks might also be impaired in the presence of a secondary calculation task. Hence, it remains to be resolved whether previously reported operation type specific interactions could be accounted for by non-operational factors like difficulty or response mode.

To answer if previously reported differential interactions would persist when difficulty and response modes of different operations and working memory tasks are stringently controlled for, we tested thirty-two participants under a dual-task regime. Half of the participants were assigned to the subtraction group whereas the other half was assigned to the multiplication group. The experiment consisted of five blocks that were randomly ordered for each participant: calculation, phonological working memory, visuospatial working memory (single task blocks), phonological working memory with calculation and visuospatial working memory with calculation (dual task blocks). Importantly, the same response mode

(verification) was used for both working memory tasks. Furthermore, two levels of difficulty were chosen for each working memory task based on a psychophysical procedure that was run before the main experiment.

In the single phonological block, participants were given a string of consonants. They were asked to keep this string of letters in mind and compare with a second string displayed 7s later. In half of the trials, sample and test string had the same ordering of letters whereas in the other half, some letters were swapped. The sample string was written in capital letters while the test was written in small letters. This ensured that participants decided based on phonological working memory and not visual similarity. In the phonological dual task block, participants were given a calculation problem (subtraction or multiplication depending on the group) in between the sample and test string.

In the single visuospatial block, participants were given a 5 × 5 grid on which some locations were filled with circles. They were asked to keep this layout in mind and compare it with a second layout displayed 7s later. In half of the trials, sample and test grid had the same locations marked whereas in the other half, they were different. Again, in the visuospatial dual task block, participants were given a calculation (subtraction or multiplication depending on the group) in between the sample and test grid.

Finally, calculation blocks consisted of two alternative forced choice task. One-digit × one-digit or one-digit × two-digit multiplications and two-digit – two digit subtractions were used. Importantly, a different list of calculations was used in each block with calculation (single calculation, phonological dual task and visuospatial dual task) and problem size was counterbalanced between operations (subtraction and multiplication) as well as between different lists.

We found that both types of operations (multiplication and subtraction) interact with

both types of working memory pathways (phonological and visuospatial). Moreover, the degree of interference between calculation and working memory depended on task difficulty. That is, we observed higher interference for higher working memory load. In addition, when we submitted the difference between dual and single task reaction times and error rates for calculations problems, there was no interaction between arithmetic operation (multiplication and subtraction) and work memory type (phonological and visuospatial), which provides evidence against the idea that different arithmetic operations rely to different degrees on either working memory system.

To sum, in contrast to previous studies proposing a dissociation between multiplication and subtraction (Lee & Kang, 2002; Lee, 2000), our results indicate that both types of operations depend on both types of working memory pathways. The interference between calculations and working memory tasks increase depending on the level of difficulty. Hence, use of multiplications with larger problem size compared to subtractions could be the reason why some previous studies reported a stronger interaction between multiplication and phonological working memory (e.g., Lee & Kang, 2002). Instead of an operation type specific dissociation in the brain, it is possible that, depending on the level of experienced difficulty, participants might be employing different strategies (e.g., more verbal or more spatial strategies). This is in line with a recent study suggesting that previously observed neural differences between arithmetic operations could be fully accounted for by strategy selection (Tschentscher & Hauk, 2014).

5.2 Study 2

Primate electrophysiology studies reported numerosity-selective neurons in the parietal cortex (Nieder & Miller, 2004). A small proportion of those numerosity-selective neurons respond in a presentation format (Nieder et al., 2006) and modality (Nieder, 2012) independent manner. However, experimental evidence for a format and modality-independent numerosity representation in humans is still lacking. While fMRI adaptation and pattern recognition studies displayed numerosity-related representation for non-symbolic simultaneous stimuli in human parietal cortex (Eger et al., 2009, 2013; Piazza et al., 2007), whether the same semantic representation exists for sequential numerosities and for different modalities (e.g., auditory) is still not known. Hence, we aimed at investigating the representation of non-symbolic sequential numerosities in visual and auditory modalities exploiting fMRI pattern recognition. Pattern recognition analysis was chosen because adaptation would have been too time-consuming in sequential format as representing a given numerosity takes much longer than simultaneous format.

We tested fourteen participants under fMRI in a sequential numerosity comparison task. Half of the numerosities were presented in visual modality (i.e., flickers) and the other half in auditory modality (i.e., beeps). In order to separate numerosity representation from response/comparison related processing, participants were asked to make a comparison only in 20% of trials (hereafter 'response trials'). In the remaining 80% of trials, participants were presented with a sequential numerosity without a further comparison demand (hereafter 'non-response trials'). Importantly, response trials were randomly interspersed such that once a numerosity stimulus was presented, participants did not know if they were going to compare this numerosity with the upcoming one or not. This was indicated by a change in the color of the fixation cross that came after the first numerosity. If the color of the fixation cross

changed from red to blue, participants were instructed to compare the numerosity before the blue fixation cross with the one after (always within the same modality). If the fixation cross stayed red until the next numerosity appeared, participants were instructed to forget about the first numerosity and concentrate on the new one (i.e., a new trial started).

Interestingly, the parietal BOLD signal increased significantly only during comparison/response phase ('response trials') but not during pure numerosity perception ('non-response trials'; Figure 5). During non-response trials, the BOLD signal increased only in corresponding sensory areas (visual cortex for visual numerosities and auditory cortex for auditory numerosities) and in the frontal cortex (A6). Although overall BOLD signal increase in the parietal cortex was not significant, the pattern of activation could still be informative about numerosity. Hence, we further conducted MVPA on non-response trials. We trained a classifier to distinguish four numerosities used in the experiment (5, 7, 11 and 16) separately for visual and auditory modalities. Interestingly, decoding was successful only in visual cortex ROIs for visual numerosities and only in auditory cortex ROIs for auditory numerosities. Yet, we could also decode sensory features of stimuli like duration and frequency from sensory ROIs making it difficult to claim a numerosity-specific representation in sensory cortices. We failed to decode numerosity in parietal ROIs.

On the other hand, as the increase in parietal BOLD signal was highly significant in response trials (i.e., comparison/response related signal), we further trained a classifier to distinguish numerosities during comparison/response phase. Interestingly, the decoding accuracy was significantly better than chance in a parietal ROI for both visual and auditory modalities. Yet, the cross-modal classification (i.e., training with auditory numerosities and testing on visual or vice versa) was not successful.

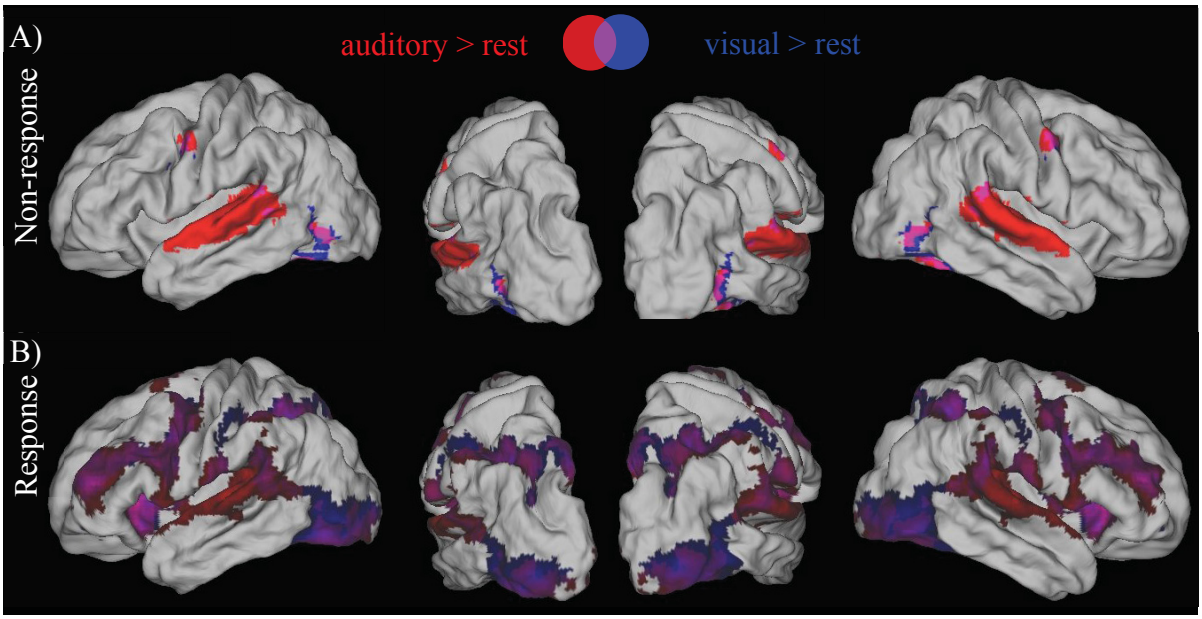

Figure 5. The BOLD signal increase in A) non-response and B) response trials separately for auditory (red) and visual (blue) numerosities (FDR corrected at p = .05, cluster level). The general linear model (GLM) model was constructed by testing all numerosities (5, 7, 11 and 16) against rest. The parietal BOLD signal increased significantly only during response trials.

To sum, our results indicate that in contrast to non-symbolic simultaneous numerosities, perception of sequential numerosities does not engage parietal circuits. The parietal cortex was involved only during comparison/response. Yet, it is very unlikely that this involvement was purely numerosity related. With the current experiment, we cannot answer what caused significant decoding in the parietal ROI as many processes are mixed within that period (e.g., comparison, decision-making, and response preparation). However, our results clearly show that pure perception of sequential numerosities does not engage the parietal cortex. Hence, it is contradicting the abstract magnitude code postulation of the TCM, which suggests that any kind of numerical information (in any format) should activate the parietal quantity circuits.

5.3 Study 3

Previous fMRI pattern recognition studies reported that the parietal cortex hosts a distributed representation of non-symbolic simultaneous numerosities (Bulthé et al., 2014; Eger et al., 2009, 2013). Yet, our study (Study 2) suggested that when comparison/response and numerosity perception are well separated, the parietal involvement disappears (Cavdaroglu, Katz, & Knops, 2015). Although all previous pattern recognition studies used a numerical comparison task, adaptation studies suggest that the parietal cortex (particularly IPS) represents numerosity even in the absence of a numerical task. Yet, fMRI adaptation and pattern recognition give different types of neural information. Adaptation goes into sub-voxel level and provides a measure of neuronal adaptation (i.e., decrease or recovery of spiking activity), whereas pattern recognition informs us about whether a representation over a larger scale (e.g., hundreds of voxels) exists or not based on the summed electrical current within a neural tissue.

It remains to be answered if a distributed representation of simultaneous numerosities exists in the parietal cortex when numerosity perception and comparison are well separated. To answer this, we investigated the representation of simultaneous (i.e., dot arrays) and sequential numerosities (i.e., flickers) exploiting fMRI pattern recognition. Going beyond previous studies, we analyzed sensory features of simultaneous numerosities as well (i.e., convex hull, total area, density and dot diameter). Hence, the questions we wanted to answer with this study were three-fold: 1) Can we replicate our previous findings about sequential numerosities? 2) Using the same design as in Study 2, can we decode numerosity in simultaneous format? 3) If so, can we decode the sensory features of simultaneous stimuli within the parietal cortex, or is the parietal representation for simultaneous stimuli numerosity-specific?

To answer the above mentioned questions, we tested seventeen participants with fMRI. They were engaged in a numerical comparison task. Half of the numerosities were presented in simultaneous format (i.e., dot-arrays) whereas the other half was presented in sequential format (i.e., flickers). Numerosity perception and comparison/response were separated using the same methodology as in Study 2 (i.e., asking participants to compare two given numerosities from the same format only at random points throughout the experiment). Furthermore, sensory features of simultaneous stimuli (convex hull, total area, density and dot-diameter) were also recorded and analyzed.

In line with Study 2, the parietal BOLD signal increased significantly only during the comparison of sequential numerosities ('response trials') but not during pure numerosity perception ('non-response trials'). On the contrary, the BOLD signal in the IPS increased for simultaneous numerosities even during pure numerosity perception ('non-response trials'). Additionally, the increase in parietal BOLD signal was significantly larger in simultaneous compared to sequential format (Figure 6). We further confirmed this dissociation between simultaneous and sequential format in the parietal cortex using MVPA. We trained a classifier to distinguish four numerosities used in the experiment (5, 7, 11 and 16) separately for simultaneous and sequential format. While the decoding accuracy for simultaneous numerosities was significant in parietal ROIs, we failed to decode sequential numerosities within the same parietal ROIs. Furthermore, we trained a classifier to distinguish the presentation format in the same ROIs where we could decode simultaneous numerosities. Interestingly, the decoding accuracy for presentation format (simultaneous vs. sequential) was also highly significant indicating a format-specific representation.

A recent fMRI study with small (2-6) auditory sequential numerosities found numerosity-related adaptation in insula (Wang et al., 2015). As we also observed a prominent increase in insular BOLD signal during the presentation of sequential numerosities (non-

response trials), we trained a classifier to distinguish numerosities in insular ROIs separately in simultaneous and sequential format. Interestingly, an opposite profile to the parietal one was observed in insula. While decoding accuracies were significant for sequential numerosities, we failed to decode simultaneous numerosities within the same insular ROIs. Furthermore, we calculated voxel-tuning profiles (akin to tuning curves in electrophysiology, but on a much larger spatial scale) per numerosity separately in simultaneous and sequential format. These were also very different for simultaneous and sequential formats (Figure 7). This might also be taken to indicate different coding schemas for sequential and simultaneous numerosities. Nonetheless, the tuning curves for voxels should be interpreted with caution as it is on a very different scale than the tuning curves from electrophysiology.

Last but not least, how numerosity is extracted from a simultaneously presented set of visual objects is still debated. Some computational models and fMRI studies suggest a dedicated mechanism for numerosity extraction with an occipito-parietal gradient from sensory representation to numerosity specificity (Dehaene & Changeux, 1993; Roggeman, Santens, Fias, & Verguts, 2011). Yet, the parietal cortex represents other sensory dimensions like object size and illumination as well (Harvey et al., 2015; Pinel, Piazza, Le Bihan, & Dehaene, 2004; Tudusciuc & Nieder, 2007). Hence, others have suggested that numerosity could be extracted from visuospatial dimensions like convex hull, total area, density or object size (Dakin, Tibber, Greenwood, Kingdom, & Morgan, 2011; Gebuis & Reynvoet, 2012b). To investigate whether visuospatial dimensions of the same stimuli – along with numerosity – can be decoded from the occipito-parietal hierarchy, we trained classifiers to distinguish convex hull, total area, density and dot-size in ROIs extracted from striate, extrastriate and parietal cortices. Interestingly, while decoding accuracies for numerosity as well as visuospatial dimensions were significant in striate and extrastriate cortices, only numerosity and object size remained significant in parietal ROIs.

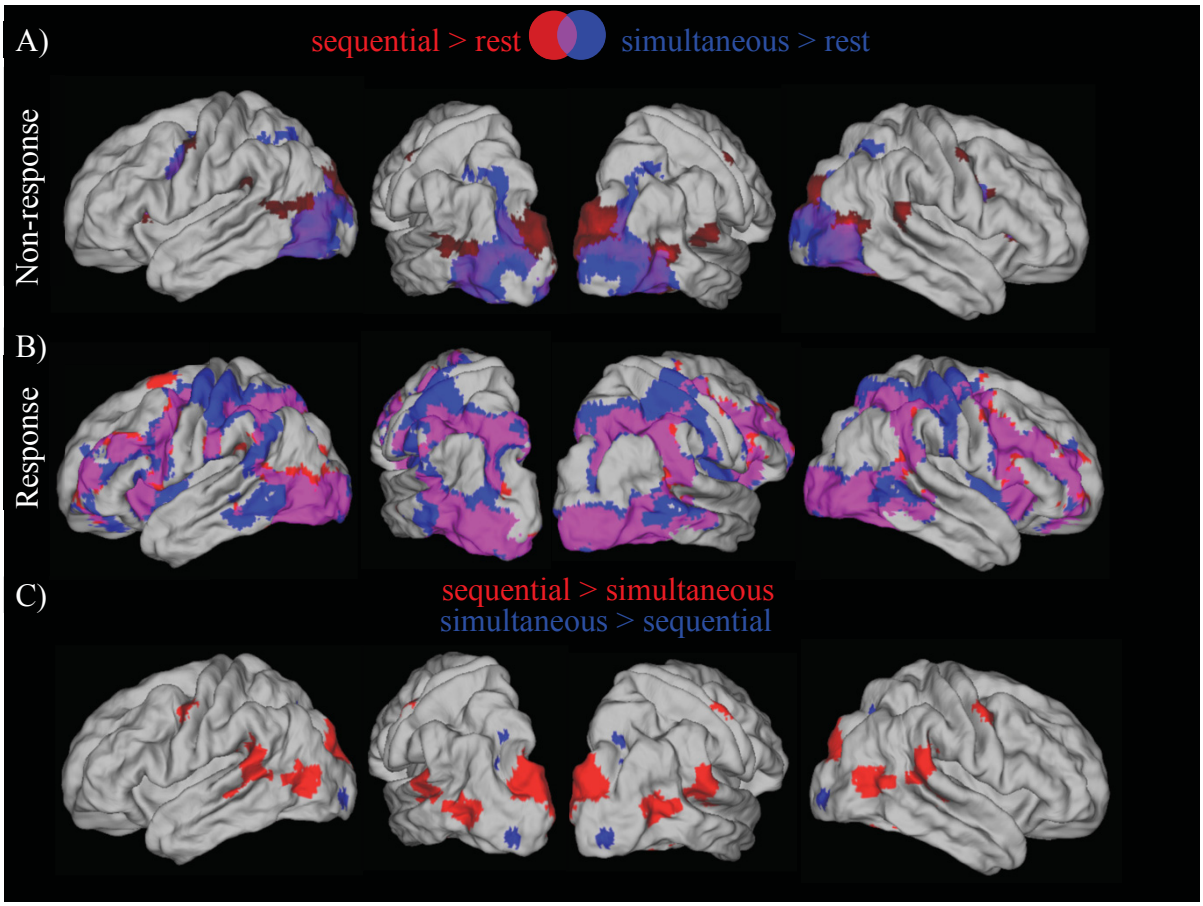

Figure 6. The BOLD signal increase in A) non-response and B) response trials separately for sequential (red) and simultaneous (blue) numerosities (FDR corrected at p = .05, cluster level). The general linear model (GLM) model was constructed by testing all numerosities (5, 7, 11 and 16) against rest. The parietal BOLD signal increased significantly only during response trials. C) Depiction of areas where BOLD signal increased significantly more in one format compared to the other. Red: sequential > simultaneous Blue: simultaneous > sequential

To sum, our results indicate that the parietal cortex is involved in the representation of non-symbolic numerosities only in simultaneous format but not sequential as confirmed by general linear model (GLM) and MVPA analysis. Furthermore, the representation of sensory dimensions decreases from visual to parietal cortex whereas numerosity stays stable, indicating a numerosity-specific representation in the parietal cortex. Although our results cannot speak directly to different models proposed for numerosity extraction, the fact that only diameter and numerosity could be decoded from the parietal ROIs suggests that the observed parietal BOLD increase is beyond pure averaging of parietal sensory signals. In

contrast to the parietal cortex, insula seems to have a role in sequential but not simultaneous format. Taken together, our results speak against TCM's suggestion that the parietal abstract magnitude code represents numerosity in a format-independent fashion.

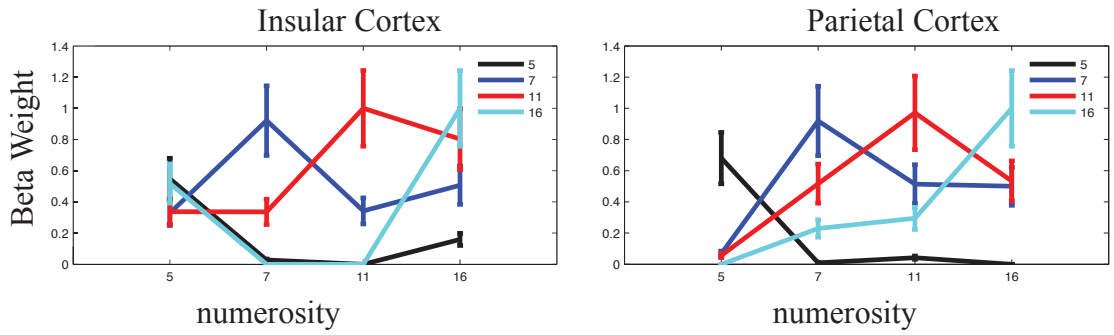

Figure 7. The voxel-tuning curves for sequential numerosities in the insular cortex (left) and for simultaneous numerositis in the parietal cortex (right). The beta weights are normalized to lie between 0-1. The color coding indicates the preffered numerosity: 5 (black), 7 (blue), 11 (red) and 16 (cyan). The insular tuning profile for sequential numerosities has a more U-shaped like funciton whereas the parietal tuning profile for simultaneous numerosities resembles more the numerosity-selective tuning curves from electrophysiology.

6 Conclusions

The current thesis explored the predictions of the TCM within the context of functional specialization in the brain. Study 1 investigated the proposed dissociation between mental subtraction and multiplication in relation to different codes and cortical pathways employed by the two operations. We demonstrated that when the difficulty of arithmetic operations (subtraction and multiplication) and working memory tasks (phonological and visuospatial) is stringently controlled for on inter and intra-subject level, and interactions between arithmetic operations and working memory pathways are studied in a reciprocal fashion, the previously claimed dissociation between operation types disappear.

Study 2 and 3 investigated the nature of the abstract magnitude code postulated by the TCM. Specifically, Study 2 investigated whether the abstract magnitude code would be employed for non-symbolic numerosities presented over time (i.e., sequential) and in different modalities (i.e., visual and auditory), even when numerosity perception and comparison are well separated in time. We demonstrated that regions that are thought to store an abstract representation of magnitude (i.e., parietal cortices and specifically bilateral IPS) are not recruited during pure numerosity perception when information is presented over time. Study 3 investigated whether the abstract magnitude code is recruited only when information is presented over space (i.e., simultaneous) but not over time (i.e., sequential) using the same design as Study 2 that separated numerosity perception from response/task related processing. We demonstrated that parietal magnitude regions suggested by the TCM are employed only for simultaneous numerosities. Furthermore, we showed that the representation of non-numerical sensory dimensions of simultaneous stimuli decrease while numerosity remains stable over visuo-parietal hierarchy supporting a numerosity-specific representation in the

parietal cortex. The implications of these results will be discussed first for the TCM, and then for functional specialization in the brain in general.

6.1 Implications for the Triple Code Model

Dehaene et al. (2003) proposed that numerical abilities can be divided into three distinct codes (verbal, Arabic and magnitude) subserved by distinct cortical pathways that interact with a superior parietal attention system. On this tripartite system, dissociations between arithmetic operations, especially between subtraction and multiplication, were claimed to exist based on neuroimaging and lesion data (Dehaene et al., 2003). Specifically, multiplication was thought to rely on the verbal code as it is solved through rote verbal memorization and phonologic elaboration while subtraction was thought to rely on the magnitude code.

Yet, previously observed dissociations can also be due to factors like difficulty, problem size or strategy selection. In line with this, our first study suggested that when the difficulty of calculation problems and working memory tasks (on which verbal and magnitude codes are thought to reside) are balanced within and between participants, both types of operations (multiplication and subtraction) interact with both working memory pathways (phonological and visuospatial). In concert with a recent fMRI study suggesting that previously observed differential activations for different arithmetic operations could be fully accounted for by particular strategies participants employ (Tschentscher & Hauk, 2014), we suggest that different neural circuits are recruited depending on the difficulty of problems (e.g., larger problems might recruit more phonological resources independent of the operation type), visuospatial and phonological capacities of the participants, and strategies they employ based on their capacities (Demir et al., 2014). Hence, our results are in agreement with the

TCM in the sense that mental calculation depends on both verbal and magnitude codes. Yet, we suggest that these codes do not support operation type specific mapping but rather they are involved in all types of arithmetic operations depending on how participants approach the problem and particular demands of the task.

It should be noted that our study, as well as previous studies in the field, were based on the assumptions of Baddeley's model of working memory (Baddeley & Hitch, 1974). That is, the abstract magnitude and verbal codes were assessed by visuospatial and phonological working memory tasks that are thought to function as independent modules in Baddeley's model. Yet, another valid interpretation of the results of *Study 1* would be that visuospatial and phonological working memory do not function completely independent from each other or from the central executive. Hence, the two-way interaction between subtraction/multiplication and visuospatial/phonological working memory could also be due to a resource sharing between working memory pathways or due to the involvement of central executive even in pure working memory tasks (i.e., that don't require manipulation of the content). It remains to be answered by future studies how valid the dual-system view of Baddeley's model of working memory is.

Another debated postulation of the TCM was the abstract magnitude code. It was suggested that the abstract magnitude code – that resides on the hIPS – represents any kind of numerical information in a format and modality independent fashion (Dehaene et al., 2003). Although primate neurophysiology research reported neurons in ventral intraparietal cortex (VIP) that are tuned to numerosity in a format (Nieder et al., 2006) and modality (Nieder, 2012) independent fashion (i.e., abstract), whether the same abstract representation of magnitude exists in humans is not known. Furthermore, the format and modality independent coding was found only for small numerosities in primates whereas a core number system, as suggested by the TCM, postulates an abstract representation of larger numerosities as well.

In Studies 2 and 3 we tested participants with fMRI in a numerosity comparison task to investigate the modality and format independence of the magnitude code, respectively. In contrast to what the TCM suggests, the parietal cortex (in particular the hIPS) was involved only when numerosities were presented in simultaneous format but not when presented sequentially. Taken together with other fMRI studies that failed to find a common representation for symbolic numbers and non-symbolic simultaneous numerosities, we suggest that the quantity representation in the hIPS is format-specific (Bulthé et al., 2014, 2015; Cohen Kadosh et al., 2007; Cohen Kadosh & Walsh, 2009; Dormal et al., 2010; Lyons et al., 2015).

To sum, our results suggest that mental calculation relies on phonological and visuospatial circuits, in line with the TCM. Yet, we suggest that the dependence on phonological vs. visuospatial circuits is related to non-operation specific factors, hence calling for a re-interpretation of the suggested dissociation between different arithmetic operations (e.g., multiplication and subtraction). Furthermore, we suggest that the representation of non-symbolic sequential numerosities depends on a different route than what the TCM suggests (i.e., the magnitude code relying on hIPS). Our results suggest a role for insula in the extraction/representation of sequential numerosities. This should be further investigated by electrophysiological methods that have better resolution than fMRI and the TCM should be updated accordingly.

6.2 Implications for functional specialization in the brain

Our results (Study 2 and 3) suggest that non-symbolic numerical information presented over space vs. over time recruit different circuits in the brain. While simultaneous

numerosities are represented in the parietal cortex, the perception of sequential numerosities does not engage the parietal cortex.

The most influential computational models that explain how simultaneous numerosities are extracted suggest three stages: normalization for object location and size, summation of the normalized activity and filtering of the summed activity by numerosity detectors (Dehaene & Changeux, 1993; Verguts & Fias, 2004). The summation of the normalized activity is thought to be represented by neurons in LIP that code for numerosity monotonically (Roitman et al., 2007). The LIP neurons also code for the saliency information in a visual scene. That is, they guide visuospatial attention by coding for the saliency of objects in their receptive field (Bisley & Goldberg, 2010). Hence, although speculative, repetitively presenting the same objects in the same location might render LIP neurons unresponsive. Therefore, the parietal circuitry might not be suitable to represent information that is presented without saliency content, even within a numerical context.

To conclude, numerical abilities might have been developed by coopting parietal saliency circuits as suggested by recent studies and computational models in line with the idea of neuronal recycling (Dehaene & Changeux, 1993; Dehaene & Cohen, 2007; Knops et al., 2014; Roggeman et al., 2011). Yet, the same mechanism falls short at explaining how numerosity is extracted when there is no spatial saliency content (i.e., when numerical information is represented sequentially at the same location). In line with this, our results suggest a different route for the extraction of sequential numerosities. Taken together, there is evidence for a certain degree of numerical specialization in the brain as suggested by recent electrophysiology and fMRI studies (Dastjerdi et al., 2013; Eger et al., 2013; Nieder & Miller, 2004). Still, this specialization does not seem to operate on a semantic level as stimuli with the same semantic meaning yet distinct computational requirements recruited different regions in the brain in our studies. Hence, we suggest that functional specialization in the

brain might be operating based on computational similarity rather than a semantic one (Patel, Kaplan, & Snyder, 2014).

7 Future Directions

Our studies suggest that the IPS is involved only when the numerical information is presented over space but not over time. Although previous primate electrophysiology studies reported neurons in IPS that code for numerosity in sequential format as well, only small numerosities were tested in those studies so far (1-4; Nieder and Miller, 2004). As we employed fMRI, it is also possible that we failed to measure subvoxel level information or an inhibition-exhibition balance occluded the numerosity related coding in sequential format. Taken together, whether numerosity coding for large sequential numerosities exist in IPS should be further investigated with electrophysiological methods that have much better resolution than fMRI.

Moreover, as human homologue of LIP is thought to represent the saliency information in a visual scene, it is possible that presenting the numerical information at the same location (i.e., without saliency content) might have rendered these neurons unresponsive. Hence, it should be further investigated whether presenting numerosities sequentially yet in different locations would elicit parietal activity or not (i.e., presenting over time and space) in order to understand whether the lack of spatial saliency or the fact that information was presented over time lead to the current set of results.

In sequential format, numerosity related BOLD signal increase as well as a distributed representation was found in insula. Insula is known to be involved in subjective value estimation as well as time dependent processing (Uddin, 2014). Yet, we cannot conclude about the role of insula in processing sequential numerosities with our experiments. It should be further investigated with electrophysiological and imaging methods using a more detailed design addressing the exact role of insula in sequential numerosity estimation. It should also be tested whether dyscalculia patients have deficits in estimating sequential numerosities as

well. This would tell us if a parietal deficit leads to a deficiency in sequential numerosity estimation as well and provide more information about the role of the parietal cortex.

Human imaging studies in numerical cognition field concentrated heavily on the role of the parietal cortex and especially the hIPS. Primate electrophysiology reported numerosity-selective neurons in the prefrontal cortex as well (Nieder & Miller, 2004). Furthermore, prefrontal cortex plays a greater role in connecting non-symbolic numerosities to number symbols in monkeys (Diester & Nieder, 2007). Hence, the contribution of the prefrontal cortex to numerical cognition in humans should also be further investigated.

Our study (Study 3) as well as other studies successfully decoded numerosity in the visual cortex (Bulthé et al., 2014; Eger et al., 2013). Yet, primate electrophysiology studies concentrated mostly on parietal and prefrontal cortices. It is crucial to study how numerosity is extracted beginning from the retinal ganglion cells to the parietal cortex in order to answer which computational model fits better with the principles brain employs.

8 Abbreviations

IPS: Intraparietal sulcus

hIPS: horizontal aspect of the intraparietal sulcus

SPL: superior parietal lobule

LIP: lateral portion of the intraparietal cortex

VIP: ventral portion of the intraparietal cortex

AG: angular gyrus

A6: Broadmann area 6 that resides on the prefrontal cortex

fMRI: functional magnetic resonance imaging

BOLD signal: blood-oxygen-level dependent signal

GLM: general linear model

MVPA: multivariate pattern recognition analysis

ROI: region of interest

LFP: local field potentials

TCM: Dehaene's The Triple Code Model

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11 Manuscript 1

Mental subtraction and multiplication recruit both phonological and visuospatial recourses: evidence from a symmetric dual-task design

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12 Manuscript 2

Dissociating estimation from comparison and response eliminates parietal involvement in sequential numerosity perception

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13 Manuscript 3

Spatial but not temporal numerosity relies on posterior parietal cortex

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Abstract

Humans can easily extract the numerosity from a visual scene, whether the objects are distributed in time or in space (*i.e.*, format independence). Whether or not shared cortical circuits underlie sequential and simultaneous numerosity perception remains debated. Here, we used functional magnetic resonance imaging to test the format independence of visual numerosity perception. Crucially, our design allowed isolating numerosity estimation from comparison and response. We observed distinct cortical networks for sequential and simultaneous numerosities. While both simultaneous and sequential numerosities elicited overlapping BOLD response in occipital areas only simultaneous numerosities led to significant BOLD response in bilateral areas along the intraparietal sulcus. Sequential numerosities were accompanied by BOLD response in middle temporal and insular cortex. Multivariate pattern analysis revealed numerosity selectivity in parietal cortex for simultaneous but not sequential numerosities. In contrast, we found better-than-chance decoding of sequential but not simultaneous numerosities in insular cortex. Further analyses of numerosity preference at the voxel level revealed peaked numerosity tuning functions in parietal cortex, implying a labeled line coding of simultaneous numerosity. Insular cortex was characterized by a markedly different numerosity profile. Our results suggest that the parietal cortex contributes to the extraction of numerosity information from space even when no response-related processing is required. Sequential numerosity perception, on the other hand, recruits a distinct network of cortical regions.

Significance statement

A prominent proposal holds that abstract mathematical capacities are grounded in our ability to perceive the number of items in a visual scene. Therefore, understanding the scope and coding principles of this 'number sense' is crucial to elucidate the cognitive mechanisms underlying our mathematical capacities. Here, for the first time, functional magnetic resonance imaging was used to test the notion that overlapping neural circuits are involved in the perception of simultaneous (*e.g.*, dot arrays) and sequential numerosities (*e.g.*, dot flickers). Bilateral parietal cortex was activated during the perception of simultaneous but not sequential numerosities while bilateral insula was activated during sequential numerosity perception. Our results imply different coding schemes underlying simultaneous and sequential numerosity perception.

74 **Introduction**

75 Humans as well as other animals are endowed with the capacity to extract the numerosity
76 (*i.e.*, number of objects) of a given visual scene (Cantlon et al., 2009). It has been suggested
77 that symbolic mathematics crucially rely on this capacity (Halberda et al., 2008; Piazza,
78 2010). A thorough understanding of high level human abilities like symbolic mathematics and
79 their dysfunctions such as developmental dyscalculia remains elusive without resolving the
80 neural basis of this capacity. Yet, the exact nature and characteristics of numerosity coding
81 remain debated.

82 One key aspect of the mental representation of numerical magnitude that has been
83 discussed controversially is the notion of an abstract, that is format and modality independent
84 number representation (Cohen Kadosh and Walsh, 2009). Human imaging studies of
85 numerosity perception repeatedly revealed activations in the intraparietal sulcus (IPS) in tasks
86 employing different presentation formats (*e.g.*, non-symbolic dot-arrays and Arabic numerals;
87 Piazza et al., 2007) and modalities (*e.g.*, auditory or visual; Eger et al., 2003). Behaviorally,
88 numerosity adaptation across modalities in human observers suggests a generalized sense of
89 numbers (Arrighi et al., 2014). Furthermore, electrophysiology studies reported number-
90 selective neurons in the IPS of non-human primates that code for numerosities from 1-5
91 independent of presentation format (Nieder et al., 2006) and modality (Nieder, 2012). In sum,
92 these results suggest that the horizontal aspect of the IPS codes for numerosity in a
93 presentation format and modality-independent fashion, often referred to as the 'number sense'
94 (Nieder & Dehaene, 2009).

95 On the other hand, symbolic and non-symbolic number primes have been shown to
96 elicit differential latency profiles in naming tasks, pointing to disparate coding schemes
97 underlying different formats (Roggeman et al., 2007). Furthermore, when response related
98 factors are controlled for in human imaging studies, the parietal involvement in numerical

tasks vanishes (Göbel et al., 2004; Shuman and Kanwisher, 2004; Cavdaroglu et al., 2015). While fMRI adaptation and pattern recognition studies suggest also a response independent parietal contribution to the representation of symbolic and non-symbolic simultaneous numerosities (Piazza et al., 2007; Eger et al., 2009; Bulthé et al., 2014), how humans extract and represent sequential numerosities is still unresolved.

In addition, the parietal involvement in linking perception to action is not limited to representing numerical features of a given scene. Because parietal cortex codes for various non-numerical spatial dimensions like object size and illumination as well (Pinel et al., 2004; Tudusciuc and Nieder, 2007; Harvey et al., 2015), some consider numerosity a secondary feature that is extracted from spatial features like total area, density or object size (Dakin et al., 2011; Gebuis et al., 2014). Although numerosity studies control for sensory dimensions of stimuli to ensure that participants cannot rely on a single sensory feature to extract numerosity (see Dehaene, Izard, & Piazza, 2005 for a discussion), manipulating visual properties of non-symbolic simultaneous numerosities affect participants' judgments (Gebuis & Reynvoet, 2012). This indicates that numerosity perception is not completely independent from sensory dimensions.

In contrast, others argue that numbers are sensed directly, and independently of density, for example (Burr and Ross, 2008; Anobile et al., 2014). In line with the latter view neurofunctional evidence points to an occipitoparietal gradient for numerosity processing in humans (Roggeman et al., 2011). As activity travels from occipital to parietal sites, spatial features of the scene decrease in importance while numerical dimensions increase. In combination with recent empirical findings suggesting that a common spatial priority map architecture underlies visual working memory and enumeration (Knops et al., 2014), one may wonder whether the same system, that is initially spatial, can be recruited to represent

numerical information that is scattered over time (*i.e.*, sequential) rather than space (*i.e.*, simultaneous).

In this fMRI study, we tested the notion of an abstract, response-independent numerosity representation operating at the apex of an occipital-parietal gradient by presenting participants with simultaneous and sequential non-symbolic numerosities.

Materials and Methods

Participants

Twenty healthy right-handed participants underwent fMRI scanning after giving written informed consent. Three of them were excluded from further analysis due to excessive motion or abortion of the experiment. The data from the remaining seventeen participants were analyzed subsequently (8 males, mean age 27.35, SD = 4.64). All had normal or corrected-to-normal vision and reported no history of neurological or psychiatric diseases. The study was approved by Bernstein Center for Advanced Neuroimaging (BCAN, Nr. 165) and the Ethical committee of Humboldt Universität zu Berlin. Participants were reimbursed 24 €.

Stimuli

Participants were engaged in a non-symbolic numerosity-processing task. The numerosities were presented on a black background using white dots either as dot-arrays (simultaneous/over-space) or flickers (sequential/over-time). Four numerosities (5, 7, 11, and 16) outside the subitizing range were used. These numerosities were chosen as they had approximately equal distance from each other on logarithmic scale. Simultaneous numerosities were created using a set of Matlab (MathWorks) scripts as described in Dehaene

et al. (2005). The scripts were adapted such that the sensory properties of dot arrays (*i.e.,* convex hull, density, diameter and total area) were written out during stimulus creation. Sequential numerosities were created using the method described in Cavdaroglu et al. (2015).

The non-numerical sensory features of simultaneous numerosities (*i.e.,* dot-arrays) were controlled by creating two sets. In one set, the dot-size was kept constant whereas in the other set total area was kept constant. This way, the intensive (*e.g.,* dot size and inter-item spacing) and extensive (*e.g.,* total luminance and total area) features of stimuli were balanced over the whole stimulus set (see Dehaene et al., 2005 for a discussion).

The non-numerical sensory features of sequential numerosities (*i.e.,* flickers) were controlled by creating four sets. Single dot duration and total duration increased with numerosity in set 1 and decreased with numerosity in set 4. The interval between dots (IDI) increased with numerosity in set 2 and decreased with numerosity in set 3. Frequency (numerosity divided by total duration) increased with numerosity in sets 3 and 4 and decreased with numerosity in sets 1 and 2. Hence, participants could not rely on a single sensory cue (*i.e.,* duration, frequency or IDI) to extract numerosity. The individual dots were presented for a maximum duration of 270ms to prevent counting. Only in set 4 we used dot durations longer than 270ms as well. It was not possible to have a set of trials where total duration decreases with numerosity otherwise. This threshold was chosen based on previous studies which showed that participants cannot rely on verbal strategies (*e.g.*, counting) within this time frame (*e.g.,* Piazza et al., 2006; Tokita and Ishiguchi, 2011). Random jitters were introduced within flickers to prevent periodicity. The length of the jitter depended on the single dot duration. It was calculated such that after the subtraction of that jitter, the duration of the single dot was 40ms (*i.e.,* jitter = [dot duration − 40ms]). This procedure guaranteed that 1) each individual dot remained distinguishable from the previous or subsequent dot and 2) when the duration of a single dot was longer than 270ms, participants could not reliably count because the remaining stimuli in the sequence would still appear at a sufficiently high

presentation rate to prevent counting. The size of dots was constant for a given sequence and was chosen randomly from a file that kept the total area occupied by each dot-array in simultaneous stimuli. This ensured by and large balanced illumination between simultaneous and sequential numerosities.

Stimuli were generated and presented using Matlab (MathWorks) and Psychtoolbox (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007) and were projected with an LCD projector onto a translucent screen in the bore of the scanner and viewed through a mirror mounted on the head coil. The duration of each dot and IDI in sequential stimuli was calculated as multiples of the refresh rate of the monitor (60Hz) and the presentation of all the dots was synchronized with vertical refresh of the projector.

Experimental Task and Design

To separate decision and response related activations from numerosity perception participants responded only in one third of trials (henceforth 'response trials'). In response trials, two numerosities from the same format were presented (*i.e.,* simultaneous vs. simultaneous or sequential vs. sequential). Participants indicated via left (first) or right (second) button press which of two subsequently presented numerosities was numerically larger. The comparison numerosities were either 25% larger or smaller than the main numerosities in order to balance difficulty across numerosities. In the remaining two thirds of trials, only one numerosity was presented and no response was required (henceforth 'non-response trials').

Upon presentation of a given numerosity, participants did not know whether or not they would have to make a comparison with that numerosity later on. This information was given only after they were exposed to the numerosity. If the color of the fixation-cross that came after the numerosity changed from red to blue, they had to compare the numerosity before the blue fixation-cross with the numerosity after (*i.e.,* response trials). If the fixation-

cross stayed red until the next numerosity appeared, they were instructed to forget the previous numerosity and concentrate on the new one (*i.e.,* non-response trials, Figure 1). This way, we encouraged participants to pay attention to the numerical dimension of stimuli at all times without having any comparison or response related confounds in numerosity perception.

<<Figure 1>>

The experiment had a fast-event related design. The timing of stimuli was optimized using simulation with fMRI design software (efMRI V9) and a stochastic design (http://www.mccauslandcenter.sc.edu/CRNL/tools/fmrisim). This type of design allows for shorter scanning periods with greater statistical power than deterministic designs (*i.e.,* fixed interstimulus interval-ISI) or purely random ISIs (Dale, 1999; Friston et al., 1999). The order of conditions and the length of the ISI were determined using an exponential function (Dale, 1999). Specifically, the ISI was randomized from an exponential distribution, taking into account the minimum ISI of 4000ms, maximum ISI of 9000ms and an average ISI of 6000ms (Friston et al., 1999). The time of the jittered fixation cross was adjusted accordingly. Double-Gamma hemodynamic response function (HRF) emulation was used to emulate the SPM HRF. Five conditions were entered into the software to get the optimized presentation time for simultaneous non-response, simultaneous response, sequential non-response, sequential response and null event (*i.e.,* fixation) trials. Within each condition, trials were randomly distributed between four numerosities used in the experiment (*i.e.,* 5, 7, 11, and 16).

The duration of null events was fixed at 1.4s which was the average duration of all trials. The dot-arrays (*i.e.,* simultaneous numerosities) were presented for 200ms. The flickers (*i.e.,* sequential numerosities) had a total duration between 630 and 4870ms. The duration of the fixation cross (ISI) after each response trial changed in between 4071 and 8872ms and was determined by efMRI software as mentioned above. The duration of the fixation cross

between the first and second numerosity in response trials was chosen randomly from ISIs used in between trials. The experiment consisted of eight blocks in total. In each block, there were sixty-four non-response trials (half simultaneous), thirty-two response trials (half simultaneous) and eight null events which lasted in total around ~9mins. Hence, the total duration of the main fMRI task was ~72mins.

In non-response trials, an equal number of trials were drawn from each stimulus set. That is, in one block, there were sixteen numerosities from each simultaneous set and eight numerosities from each sequential set. In response-trials, an equal number of trials were drawn from each stimulus set for the first numerosity. Importantly, the first and second numerosities were always drawn from different sets to make sure that participants could not rely on non-numerical sensory features while they were comparing the two numerosities. Furthermore, both response and non-response trials had an equal amount of trials per numerosity and an equal amount of stimuli was drawn from each set.

Localizer Task

To independently determine functional ROIs for multivariate analysis, a 12 minutes functional localizer was created using Psychtoolbox (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007) and presented after the numerical task. The task is an adapted version of the localizer described in Cavdaroglu et al. (2015) with an additional visual motion localizer appended. It consisted of reading, date recall, mental subtraction, object grasping, house roof color naming, saccade formation, motion and rest conditions.

Reading, subtraction and date recall conditions were presented using an optimized rapid event related design (see Cavdaroglu et al., 2015 for all the details about timing). Ten simple sentences ("Bears are fond of salmon and honey"), subtraction problem sentences ("Calculate eleven minus five") (translated from Pinel et al., 2007) and novel date recall sentences ("The date of New Year's Eve is ____"), were intermixed with ten rest periods, for

a total of 40 trials. In all three conditions, participants were instructed to silently read the sentences and mentally generate an answer when necessary (subtraction and date recall) without giving an explicit response. In the rest condition, a blank screen with a central fixation dot was presented.

Object grasping, saccades and roof color naming blocks were presented using an optimized epoch design. Black and white illustrations of graspable objects (*e.g.*, scissor, cup; courtesy of Philippe Pinel), multidirectional (360°) saccade targets and photographs of houses with different roof colors, were presented. In object grasping trials, participants were instructed to mentally imagine grasping the objects with their dominant (right) hand. In saccade trials, three saccades were made by following a saccade target (+). In house roof color naming, participants were instructed to silently name the roof color. All trials were alternated with jittered fixation trials.

The visual motion localizer was added as we found increases in the BOLD signal in MT during processing of non-symbolic numerosities in a previous experiment (Cavdaroglu et al., 2015). It was based on the MT localizer described in Takemura et al. (2012). Two hundred white dots (0.25°) were presented on a black background with a circular aperture of 20° diameter centered at the fixation point. In a 12s motion block, the dots moved inwards and outwards at a speed of 8°/s. The motion block was followed by a 12s stationary block. Each dot lasted for 10 frames and it was replaced at a random position once the life time ended. Moreover, the dots that crossed the borders of the circle during outward motion were replaced at random locations within the circle as well as the dots that reached the central fixation during inward motion. Nine pairs of motion and non-motion blocks were run in total.

fMRI data acquisition

Functional images were acquired at the Berlin Center for Advanced Neuroimaging (BCAN) with a 3T Siemens TIM Trio scanner (Siemens, Erlangen), using a 12-channel head coil.

Before the experiment, a T1-weighted image (MPRAGE) was collected as high resolution anatomical reference (TR = 1900ms, TE = 2.52ms, flip angle = 9°, FOV = 256mm × 256mm × 192mm, resolution = 1mm). T2* -weighted gradient-echo echo-planar images were collected during the main experiment (TR = 2500ms, TE = 25ms, flip angle = 82°, FOV = 190mm × 190mm, resolution = 2.5mm, slices = 42 slices with a 20% distance factor; interleaved acquisition order). Finally, T2*-weighted gradient-echo echo-planar images were collected during the localizer task (TR = 2000ms, TE = 30ms, flip angle = 78°, FoV = 192mm × 192mm, resolution = 3mm, slices = 33 with a 25% distance; descending acquisition order). The first two images in each series served to guarantee stable magnetization and were not recorded. After the acquisition of the anatomical image as well as before the localizer, a magnetic field mapping sequence was run to correct for inhomogeneities in the magnetic field (TR = 400ms, TE = 5.19ms/7.65ms, flip angle = 60°, FOV = 192mm × 192mm, resolution = 3mm, slice gap = 25%, slices = 33).

fMRI data analysis

Images were analyzed using Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/). Functional images were first reoriented to the anatomical reference and then corrected for inhomogeneities in the magnetic field. Subsequent preprocessing included slice-timing correction (where middle image in the time series was taken as the reference), spatial realignment and unwarping, co-registration to the unwarped mean image, segmentation, normalization to standard Montreal Neurological Institute (MNI) space and smoothing (FWMH = 6 × 6 × 6mm).

After preprocessing, a general linear model (GLM) based on numerosity was defined using a canonical HRF. The numerosity model included a regressor for each numerosity (5, 7, 11 and 16); separately for simultaneous/sequential formats and response/non-response trials as well as a regressor for null events. In response trials, the first and second numerosities were

also modeled separately. Thus, the numerosity-GLM had 33 regressors in total along with 6 movement parameters from preprocessing to capture signal variations due to head motion. The event-related numerosity regressors were locked to the onset of the numerosity presentation. The null events were used as baseline for the contrasts in univariate analysis.

Unsmoothed images from the preprocessed data were used for multivariate analysis to preserve the maximal amount of spatial information. Pattern classification was performed using linear support vector machines (SVM, LIBSVM 3.12, Chang and Lin, 2011) on The Decoding Toolbox (Hebart et al., 2015). The regularization parameter [C] was set to 1. A one-block-out cross validation scheme was employed. That is, one experimental block was left as the test data and the remaining seven blocks were used to train the classifier. The left-out block was iterated over all eight blocks and an average decoding accuracy estimate was obtained at the end.

In order to investigate how numerosity-specific the pattern recognition results were in simultaneous trials, the stimuli were re-organized for each sensory feature (*i.e.,* convex hull, density, diameter and total area) such that there were four categories for the respective sensory feature. That is, instead of labeling the dot arrays based on the number of dots (*i.e.*, 5, 7, 11 and 16), we labeled them with the corresponding category (*e.g.*, based on how big the total area is) in four different models that were based on the convex hull, total area, density or diameter of the dots in the stimulus. Since perfect balancing of the number of trials in each category was not possible in all cases, we corrected for the remaining numerical imbalances between different categories by using the balanced accuracies (that are provided by The Decoding Toolbox) during the statistical testing of multivariate analysis results for sensory features.

Analysis of the localizer data and ROI extraction

Preprocessing of the localizer data was identical to the functional data besides the reference slice used for slice-timing correction (first image) and the order of slice-timing correction and spatial alignment (here, spatial alignment and unwarping was performed before slice-timing correction). After preprocessing, the localizer task was modeled by a canonical HRF and a GLM was defined that included a regressor for each condition (houses, objects, dates, reading, subtraction, saccades, motion and fixation) and 6 motion parameters from preprocessing to capture signal variations due to head motion.

For multivariate pattern analysis, bilateral parietal ROIs were extracted from the combination of F-contrast (main task) on a subject-by-subject basis and subtraction minus reading contrast (localizer task) on group level within a mask of parietal cortex (WFU PickAtlas, Maldjian et al., 2004, 2003). Within these masks, the 500 most active voxels were chosen as subjective ROIs (Figure 2a). The group level subtraction minus reading contrast was used as there were not enough voxels for most subjects on individual level. Moreover, as we observed it in this experiment and a recent study that used sequential auditory numerosities reported an increase in BOLD signal in the insular cortex (Wang et al., 2015), we extracted one main insular ROI from the F-contrast (main task) on a subject-by-subject basis within a bilateral mask of insular cortex (WFU PickAtlas, Maldjian et al., 2004, 2003). Again, the 500 most active voxels within these masks were chosen as subjective ROIs (Figure 2b).

<<Figure 2>>

Finally, to investigate how the representation of numerosity and other sensory features evolve along the visual hierarchy, we created two ROIs separating striate from extrastriate areas of the visual cortex. The first visual ROI was a combination of houses minus rest contrast (localizer task) on subject-by-subject basis within a mask of occipital cortex minus

striate cortex (Anatomy Toolbox, Eickhoff et al., 2007, 2006, 2005; Figure 3a). The second visual ROI was a combination of houses minus rest contrast (localizer task) on a subject-by-subject basis within a mask of striate cortex (V1, WFU atlas, Maldjian et al., 2004, 2003; Figure 3b). Hence, the first visual ROI included the extrastriate areas whereas the second visual ROI included only the striate cortex. For both of these ROIs, the 500 most active voxels within these masks were chosen as subjective ROIs.

<<Figure 3>>

Results

Behavioral Results

The mean accuracy was 79.46% (SD 8.52%) for simultaneous response trials and 72.67% (SD 6.75%) for sequential response trials. In both formats, participants performed significantly above chance ($t_{(16)} = 14.238$, $p < 0.001$ for simultaneous and $t_{(16)} = 13.852$, $p < 0.001$ for sequential). We submitted behavioral accuracies to a repeated measures ANOVA with factors format (simultaneous, sequential) and numerosity (5, 7, 11 and 16) and found a main effect of format ($F_{(1,16)} = 13.761$, $p = 0.002$), numerosity ($F_{(1,16)} = 16.271$, $p < 0.001$) as well as an interaction between format and numerosity ($F_{(1,16)} = 5.034$, $p = 0.004$). Post-hoc tests revealed that in simultaneous trials, the comparison accuracy for numerosity 7 was significantly higher than the accuracy for numerosity 16 ($t_{(1,16)} = 5.22$, $p = 0.001$; Bonferroni corrected). In sequential trials, comparison accuracies for numerosity 7 and 11 were significantly higher than for numerosity 5 ($t_{(16)} = 5.912$, $p = 0.009$; $t_{(16)} = 5.748$, $p < 0.001$ respectively; Bonferroni corrected) and the accuracy for 11 was significantly higher than 16 ($t_{(16)} = 4.188$, $p = 0.005$; Bonferroni corrected). Participants were significantly more accurate in simultaneous compared to sequential response trials ($t_{(16)} = 4.485$, $p < 0.001$).

fMRI Results

Univariate analysis

The BOLD signal during non-response trials was captured by contrasting all numerosities against baseline, irrespective of numerosity and separately for simultaneous and sequential trials. For simultaneous numerosities in non-response trials, BOLD signal increased significantly in bilateral visual areas, bilateral intraparietal lobule, left-hemispheric superior parietal lobule and bilateral frontal gyrus (Figure 4a and Table 1). For sequential numerosities in non-response trials, BOLD signal increased significantly in bilateral primary visual areas, right-hemispheric superior temporal sulcus, bilateral insula and precentral gyrus, and right-hemispheric BA 44 (Figure 4a and Table 1). Only in the frontal cortex (BA 44) and visual cortex (V5 and Area 18) did the BOLD signal increase when we inclusively masked simultaneous and sequential non-response trials (Table 2). Furthermore, parietal areas survived when we subtracted sequential numerosities from simultaneous (Figure 4b, Table 3).

The BOLD signal for response trials was captured by contrasting the second numerosity in response trials against non-response trials separately for simultaneous and sequential format. As the comparison (and response) came right after the presentation of the second numerosity, this contrast included comparison/response related activity. The BOLD signal increased prominently in the parietal cortex (as well as other areas) for response trials both in simultaneous and sequential format (Figure 4c). All the contrasts reported in this paper were corrected with FDR at $p = 0.05$ on cluster level using xjView (http://www.alivelearn.net/xjview).

<<Figure 4>>

<<Table 1>>

<<Table 2>>

<<Table 3>>

We further checked the conjunction of subtraction and saccade related activity from the localizer task with the activity in simultaneous non-response trials within a mask of parietal cortex (WFU PickAtlas, Maldjian et al., 2004, 2003). We observed an overlap between saccade, subtraction and simultaneous numerosity-related BOLD signal in posterior portions of the IPS (Figure 5).

<<Figure 5>>

Multivariate analysis

We submitted the decoding accuracies to a repeated measures ANOVA with factors format (simultaneous, sequential) and ROI (parietal, insular) and found an interaction between format and ROI ($F_{(1,16)} = 5.150$, $p < 0.037$). Follow-up t-tests revealed that the decoding accuracy in the parietal cortex was significantly higher than the decoding accuracy in insula for simultaneous numerosities ($t_{(16)} = 4.127$, $p = 0.001$; Figure 2c; see Figure 2d for the confusion matrix). Other comparisons did not reach significance.

To further test whether the decoding accuracies in parietal and insular cortices were significantly different from chance classification, we ran a permutation analysis with 1000 cycles where the labels of training data were shuffled and randomized. We tested the obtained average accuracies per participant against the accuracies from the permutation analyses for both formats (simultaneous and sequential) and ROIs (parietal and insular). While the decoding accuracy for simultaneous numerosities was significantly higher than chance only in the parietal ROI (Parietal: $t_{(16)} = 2.25$, $p = 0.039$; Insular: $t_{(16)} = -2.07$, $p = 0.055$), the decoding accuracy for sequential numerosities was significantly higher than chance only in the insular ROI (Parietal: $t_{(16)} = 0.44$, $p = 0.66$; Insular: $t_{(16)} = 2.14$, $p = 0.04$).

To further investigate how the distributed representation of simultaneous numerosity evolves from the visual cortex to the parietal cortex and how numerosity-specific it is, we submitted the decoding accuracies for sensory features and numerosities into a repeated measures ANOVA comprising the factors measure (convex hull, density, diameter, total area and numerosity) and ROI (striate, extra-striate and parietal cortex). We found no main effects or interactions (Figure 3).

To test whether the decoding accuracies in visual and parietal cortices were significantly different from chance classification, we run a permutation analysis with 1000 cycles where the labels of training data were shuffled and randomized. We tested the obtained average accuracies per participant against the accuracies from the permutation analyses for all measures (convex hull, density, diameter, total area and numerosity) and ROIs (striate, extrastriate, and parietal). Decoding accuracies for numerosity and diameter were significant in all the ROIs (numerosity: $t_{(16)} = 2.39$, $p = 0.03$; $t_{(16)} = 2.6$, $p = 0.02$; $t_{(16)} = 2.24$, $p = 0.03$; diameter: $t_{(16)} = 5.5$, $p < 0.001$; $t_{(16)} = 4.46$, $p < 0.001$; $t_{(16)} = 3.92$, $p = 0.001$ for striate, extra-striate and parietal cortex respectively). Decoding accuracies for total area and density were significant only in striate and extrastriate areas (total area: $t_{(16)} = 3.36$, $p = 0.004$; $t_{(16)} = 3.6$, $p = 0.002$; $t_{(16)} = 0.667$, $p = 0.51$; density: $t_{(16)} = 3.88$, $p = 0.001$; $t_{(16)} = 3.79$, $p = 0.002$; $t_{(16)} = 1.45$, $p = 0.167$ for striate, extra-striate and parietal cortex respectively). Finally, decoding accuracies for convex hull were significant only in the striate visual cortex ($t_{(16)} = 4.02$, $p < 0.001$; $t_{(16)} = 1.45$, $p = 0.17$; $t_{(16)} = 0.68$, $p = 0.51$ for striate, extra-striate and parietal cortex respectively).

In order to investigate if any of the ROIs had a format-independent representation, we tested whether the classifier was able to discriminate presentation formats (simultaneous and sequential). Again, we statistically validated the resulting accuracies against the accuracies obtained from the permutation analysis with 128 cycles –which was the highest possible amount of permutations- where labels of training data were shuffled and randomized.

Interestingly, decoding accuracies for presentation format were significantly above chance in all the ROIs tested (striate: $t_{(16)} = 24.87$, $p < 0.001$; extrastriate: $t_{(16)} = 15.93$, $p < 0.001$; insula: $t_{(16)} = 5.61$, $p < 0.001$; parietal: $t_{(16)} = 5.15$, $p < 0.001$) indicating separate representations for simultaneous and sequential numerosities.

Tuning profiles

Previous results found number selectivity at different cortical levels. Single unit recordings in non-human primates revealed number selective neurons in the posterior parietal cortex that responded maximally to a given numerosity and exhibited a decreasing spike rate with increasing numerical distance between preferred and presented numerosity (Nieder et al., 2006). Similarly, ultra-high field fMRI studies revealed a topographic organization of numerosity in the posterior parietal cortex where a given portion of the brain responded maximally to a given numerosity (Harvey et al., 2013, 2015).

Here, we chose a straight-forward approach to test the idea of numerosity-selectivity on a voxel-level. Similar to the analysis of single neuron numerosity tuning (*e.g.*, Nieder, 2012), we determined for each participant and format which numerosity a given voxel responded to maximally by searching for the maximal beta weight from the above described model containing all formats and numerosities (see 'fMRI data analyses'). We assigned the respective numerosity to each voxel within the ROIs that were entered into decoding analyses. In a second step we computed the mean activity levels for all numerosities presented, separately for all voxels with identical preferred numerosity. The resulting numerosity tuning profiles are depicted in Figure 6, separately for parietal and insular ROIs.

<<Figure 6>>

480

481 Within each voxel tuned to a given simultaneous numerosity, we observed systematic
482 and significant impact of the presented numerosity on the BOLD signal as the numerical
483 distance between preferred and presented numerosity changed, that resembled the tuning
484 curves observed at the single-unit level (five: $F_{(3, 45)} = 57.87$, $p < 0.001$, $\varepsilon = 0.682$; seven: $F_{(3,}$
485 $_{45)} = 95.98$, $p < 0.001$, $\varepsilon = 0.626$; eleven: $F_{(3, 45)} = 103.27$, $p < 0.001$, $\varepsilon = 0.558$; sixteen: $F_{(3, 45)}$
486 $= 43.43$, $p < 0.001$, $\varepsilon = 0.397$, Greenhouse-Geisser corrected). Follow-up paired t-test
487 revealed that BOLD signal significantly decreased as numerical distance increased for
488 numerosities seven, eleven and sixteen (Table 4). For numerosity five, a significant difference
489 between preferred and non-preferred numerosities was observed while non-preferred
490 numerosities did not differ (Table 4).

491 For sequential numerosities in insular cortex a different pattern was observed. Again,
492 BOLD signal changed as a function of numerosity within voxels that shared a preferred
493 numerosity (five: $F_{(3, 45)} = 74.68$, $p < 0.001$, $\varepsilon = 0.528$; seven: $F_{(3, 45)} = 137.99$, $p < 0.001$,
494 $\varepsilon = 0.87$; eleven: $F_{(3, 45)} = 115.72$, $p < 0.001$, $\varepsilon = 0.654$; sixteen: $F_{(3, 45)} = 103.19$, $p < 0.001$,
495 $\varepsilon = 0.613$, Greenhouse-Geisser corrected). However, post-hoc t-tests confirmed the visual
496 impression that voxels with smallest and largest preferred numerosity were characterized by a
497 U-shaped profile while intermediate numerosities mainly showed peaks at the preferred
498 numerosities (Table 4 and Figure 6). Taken together, these results provide additional support
499 for the notion that sequential and simultaneous numerosity processing relies on different
500 cortical circuits by revealing different coding schemes within respective ROIs.

501

502 <<Table 4>>

503

504 **Discussion**

505 Whether the parietal cortex hosts a format-independent semantic representation of numerosity
506 has long been debated. Here, we tested participants in a numerosity comparison task in
507 simultaneous (*i.e.*, dots presented over space) and sequential (*i.e.*, dots presented over time)
508 formats. We found an increase in the parietal BOLD signal only during the presentation of
509 simultaneous numerosities, contradicting the idea of an abstract representation of numerosity.
510 Using multivariate pattern analysis, we successfully trained a classifier to decode
511 simultaneous numerosity from the BOLD signal in the parietal cortex, providing further
512 confirmation of numerosity selective activity in these areas. No better-than-chance
513 classification was observed for sequential numerosities in the same ROIs. These results imply
514 distinct underlying coding schemes for sequential and simultaneous numerosities. This idea is
515 further supported by significant decoding of the presentation format (*i.e.*, simultaneous vs.
516 sequential) in the parietal ROI. Sequential numerosities, on the other hand, were successfully
517 decoded in insula. Differential numerosity tuning functions for simultaneous and sequential
518 numerosities in insula and parietal ROIs suggest different mechanisms for processing of
519 simultaneous and sequential numerosities. Going beyond previous studies, we also
520 investigated how the representation of numerosity and visual features (*i.e.*, convex hull, total
521 area, density and diameter) evolve from the primary visual cortex to the parietal cortex in
522 simultaneous format. While striate and extrastriate areas gave rise to successful classification
523 of both non-numerical sensory features and numerosity, parietal ROIs allowed for decoding of
524 numerosity and dot diameter only, suggesting a higher level representation in the parietal
525 cortex beyond sensory features.

526 An influential computational model suggests three stages for numerosity extraction
527 from simultaneously presented set of objects: normalization for location and size of objects,

summation of the normalized activity, filtering of summed activity by numerosity-detectors (Dehaene and Changeux, 1993). Neuroanatomically, this is thought to correspond to a spatially variant coding in the visual cortex, spatially invariant and numerosity-sensitive coding in the lateral intraparietal cortex (LIP) and spatially invariant and numerosity-selective coding in the ventral intraparietal cortex (Nieder and Dehaene, 2009). In line with this, monotonic coding of numerosity was reported in primate LIP (Roitman et al., 2007; see Roggeman et al., 2011 for fMRI evidence). LIP is also known to contain a spatial representation of priority information in a visual scene by synthesizing top-down strategic goals and bottom-up stimulus saliency signals (Bisley and Goldberg, 2010). That is, LIP neurons code for the conspicuity of objects in their receptive field and guide attention to the most relevant position in space (Arcizet et al., 2011). In our study, numerosity selective areas in the superior posterior parietal cortex showed substantial overlap with areas that were active during saccadic eye movements. It was suggested that the priority architecture in these areas contributes to both subitizing and visual short term memory (Knops et al., 2014). The current study extends these results by pointing to a crucial contribution of these areas to the perception of numerosities beyond subitizing range and dovetail with the finding of a topographic numerosity representation in these areas (Harvey et al., 2013) and with previous reports of numerosity selectivity in putative human homologues of monkey area LIP (Eger et al., 2013). Since our task design allowed us to separate numerosity estimation from response processes, these results suggests that active numerosity perception without further response preparation or selection is sufficient to elicit parietal activity in simultaneous format. More generally, this is in line with recent studies that suggest a gradient from perception to action related coding in the intraparietal cortex as one travels from posterior to anterior portions (Caspers et al., 2013).

552 Although speculative, repetitively presenting the same object on the same location
553 might decrease the saliency of stimuli and render LIP neurons unresponsive. Consequently,
554 no numerosity information is transferred to IPS for sequential numerosities. Hence, the
555 parietal architecture might not be suitable for representing stimuli without saliency content,
556 even within the context of a numerical task. In agreement with this, two studies reported a
557 decreased involvement of the inferior IPS in visual working memory tasks when the items are
558 presented sequentially at the same location compared to when they are presented
559 simultaneously over space (Shafritz et al., 2002; Xu and Chun, 2006). That is, while the
560 representation of simultaneous numerosities could be based on visuospatial saliency maps in
561 the posterior parietal cortex as suggested by a recent study (Knops et al., 2014), extraction of
562 sequential numerosities might hinge on a different route. In line with this, we could decode
563 sequential numerosity in bilateral insula. The insular BOLD signal was also significantly
564 higher in sequential format compared to simultaneous. In fact, empirical findings suggest two
565 different attention pathways: a dorsal frontoparietal network that includes IPS for goal-
566 directed top-down attention and a ventral frontoparietal network that includes insula for
567 stimulus-driven, bottom-up attention (Corbetta et al., 2002, 2008). Being a hub in the ventral
568 attention network, anterior insula receives ascending inputs about bodily states as well as
569 external stimuli making it a good candidate for time-dependent processing (Uddin, 2014).

570 In line with the idea of 'abstract number representation', labeled line coding for
571 sequential numerosities was found in primate parietal cortex (Nieder et al., 2006).
572 Furthermore, a recent fMRI study revealed adaptation for sequential numerosities in human
573 IPS (Wang et al., 2015). Although our results seem to contradict these findings, it should be
574 noted that both of these studies employed small numerosities (1-4 and 2-6 respectively). fMRI
575 adaptation and primate neurophysiology can measure neural activity on sub-voxel level
576 whereas GLM and pattern recognition analysis measure summed activity from tens or

hundreds of voxels that contain millions of neurons (Logothetis, 2008). Furthermore, while primate neurophysiology assesses spiking activity from single neurons, fMRI BOLD signal correlates better with local field potentials (Goense & Logothetis, 2008). These render a one-to-one mapping between fMRI and neurophysiology data difficult. These results should be further investigated using neurophysiological methods to reveal whether sub-voxel level, single-neuron activity for large sequential numerosities, that might not be reflected in the BOLD signal, exist in the parietal cortex or not.

To sum up, our results suggest that the representation of non-symbolic numerosities in the parietal cortex is restricted to simultaneous format. This has important implications regarding the functional organization of the brain. While there is strong modularity for perceptual abilities like motion or face perception (Kanwisher, 2010), mathematics is a very new invention in evolutionary time scale to get its own dedicated circuitry. To explain this biological gap, Dehaene & Cohen (2007) suggested that culturally new inventions like symbolic mathematics and reading coopt evolutionarily old circuits. One of the candidates for symbolic mathematics was suggested to be spatial attention circuits in the parietal cortex (Dehaene and Cohen, 2007). Considering the strong interaction between space and number perception (Hubbard et al., 2005), it seems reasonable that symbolic mathematics was developed on spatial attention circuits in the parietal cortex. Yet, whether the same circuitry could be coopted for stimuli presented over time -without spatial variation- remains elusive. The computational principles employed to extract numerosity from both formats might differ in essence. In the end, modularization in the brain could be due to a computational similarity between different functions rather than a semantic one (Patel et al., 2014).

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741 **Figure Captions**

742

743 **Figure 1** Schema of the experimental procedure. Top panel depicts a response trial. After the
744 presentation of the first numerosity (Numerosity 1), the color of the fixation cross changed
745 from red to blue indicating that participants had to compare the numerosity before the blue
746 fixation cross (Numerosity 1) with the numerosity coming after (Numerosity 2). Participants
747 responded by pressing the right or left button while the fixation cross was green. After that, a
748 new trial started. Bottom panel depicts a non-response trial. The color of the fixation cross
749 remained red until the next numerosity appeared. Hence, the red fixation cross was later
750 replaced by a new numerosity and a new trial started. The inset depicts an example
751 numerosity stimulus in simultaneous (top) and sequential (bottom) format. Both formats
752 appeared with equal probability ($p = 0.05$).

753

754 **Figure 2** A) The parietal ROIs on a subject-by-subject basis. Left, top and right views
755 (respectively) of inflated PALS atlas from Caret (http://www.nitrc.org/projects/caret/). B) The
756 Insular ROIs on subject-by-subject basis. Left and right lateral views (respectively) of inflated
757 PALS atlas from Caret. Color coding indicates in how many participants a given voxel was
758 activated. C) The decoding accuracy in parietal and insular ROIs for simultaneous (sim, gray
759 bar) and sequential (seq, white bar) numerosities in non-response trials. D) The confusion
760 matrix for multivariate pattern analysis in parietal and insular ROIs for simultaneous and
761 sequential non-response trials.

762

763 **Figure 3** A) Extrastriate visual cortex ROIs (EC, on subject-by-subject basis) used for
764 decoding numerosity and sensory features. B) Striate visual cortex ROIs (SC, on subject-by-
765 subject basis) used for decoding numerosity and sensory features. Color coding indicates in

how many participants a given voxel was activated. Left and right dorsal views (respectively) of the inflated PALS atlas from Caret (http://www.nitrc.org/projects/caret/). C) Graphical depiction of decoding accuracies in SC (striate visual cortex), EC (extrastriate visual cortex) and PC (parietal cortex) separately for convex hull, density, diameter, total area and numerosity.

Figure 4 A) Depiction of areas where the BOLD signal increased significantly for simultaneous (blue) and sequential (red) numerosities in non-response trials. B) Depiction of areas where there was a greater BOLD increase for sequential compared to simultaneous (red) or simultaneous compared to sequential (blue) numerosities. C) Depiction of areas where the BOLD signal increased for response trials significantly more than non-response trials in simultaneous (blue) and sequential (red) format. All FDR corrected at $p = 0.05$ on cluster level. Left, top and right views (respectively) of the inflated PALS atlas from Caret (http://www.nitrc.org/projects/caret/).

Figure 5 Saccade (red), subtraction (green) and simultaneous numerosity perception (blue, non-response trials) related BOLD signal increase within a mask of parietal cortex (WFU PickAtlas; Maldjian et al., 2003, 2004). All FDR corrected at $p = 0.05$, cluster level. There is a high overlap between saccade, subtraction and numerosity related activity in the posterior parietal cortex.

Figure 6 Tuning curves (based on standardized beta weights) for voxels tuned to sequential numerosities in insular cortex (left) and simultaneous numerosities in parietal cortex (right). Error bars represent standard error of the mean.

Table Captions

Table 1 Brain regions where the BOLD signal increased significantly in simultaneous and sequential non-response trials (FDR corrected at p = 0.05, cluster level, k >15, labeling was done by Anatomy Toolbox).

Table 2 Brain regions where the BOLD signal increased significantly both for simultaneous and sequential non-response trials (FDR corrected at p = 0.05, cluster level, k >15, labeling was done by Anatomy Toolbox).

Table 3 Brain regions where the BOLD signal increased significantly more for one format compared to the other (*i.e.*, simultaneous > sequential or sequential > simultaneous; FDR corrected at p = 0.05, cluster level, k >15, labeling was done by Anatomy Toolbox).

Table 4 Results of pairwise comparisons of BOLD signal between adjacent numerosities. The comparison of preferred with non-preferred numerosities is indicated by grey background color. Significant comparisons are printed in bold font. Leftmost column indicates the preferred numerosity.

Figures

Figure 1

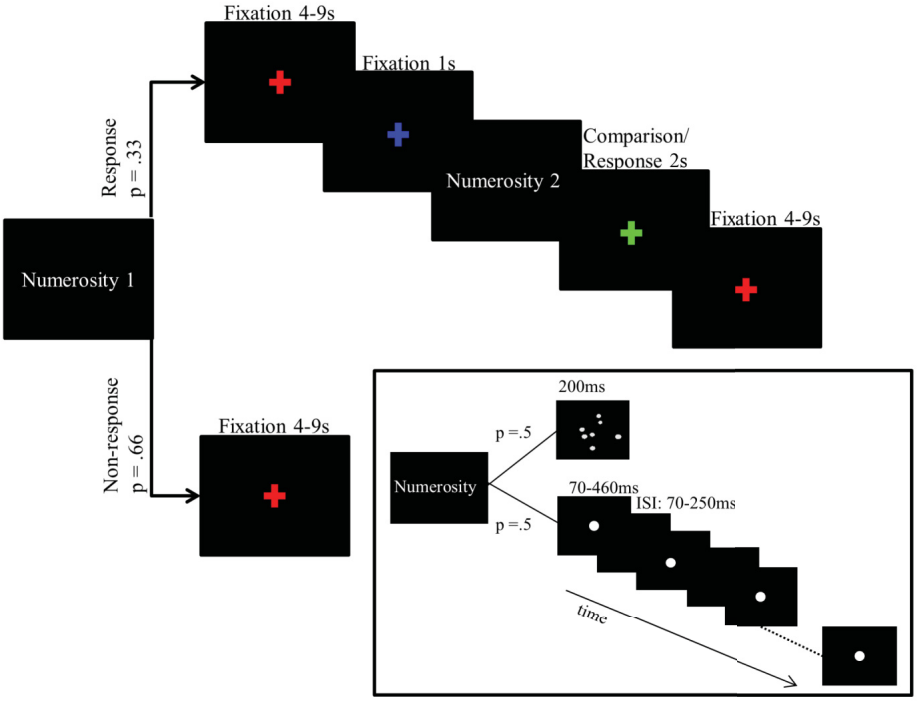
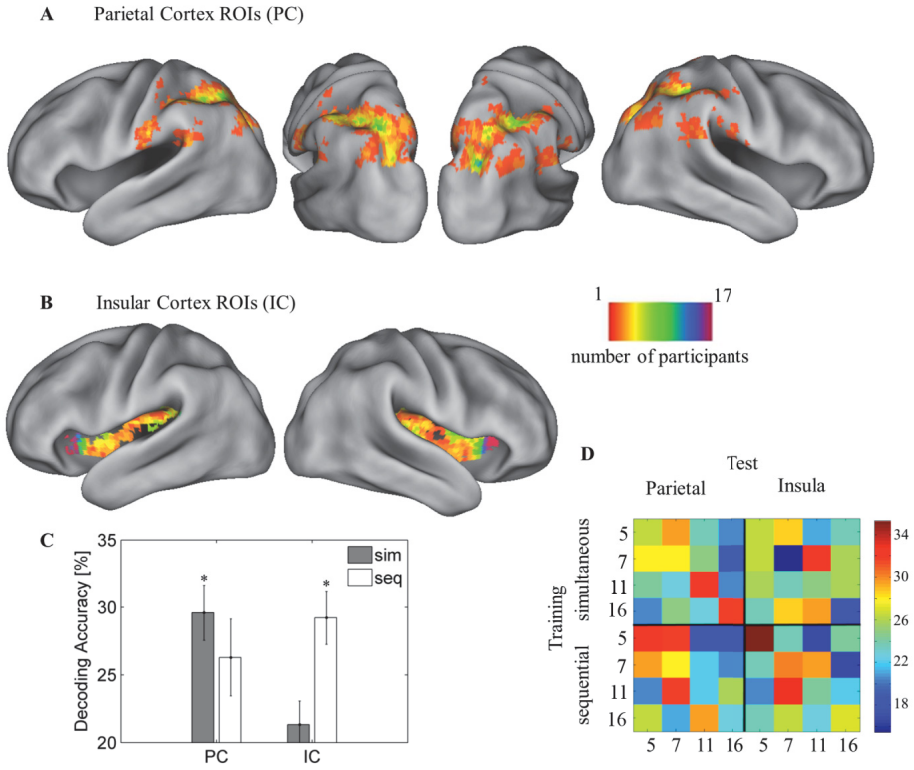


Figure 2


A
Parietal Cortex ROIs (PC)
B
Insular Cortex ROIs (IC)
1
17
number of participants
C
Decoding Accuracy [%]
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30
25
20
sim
seq
PC
IC
D
Test
Parietal
Insula
Training
simultaneous
sequential
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Figure 3

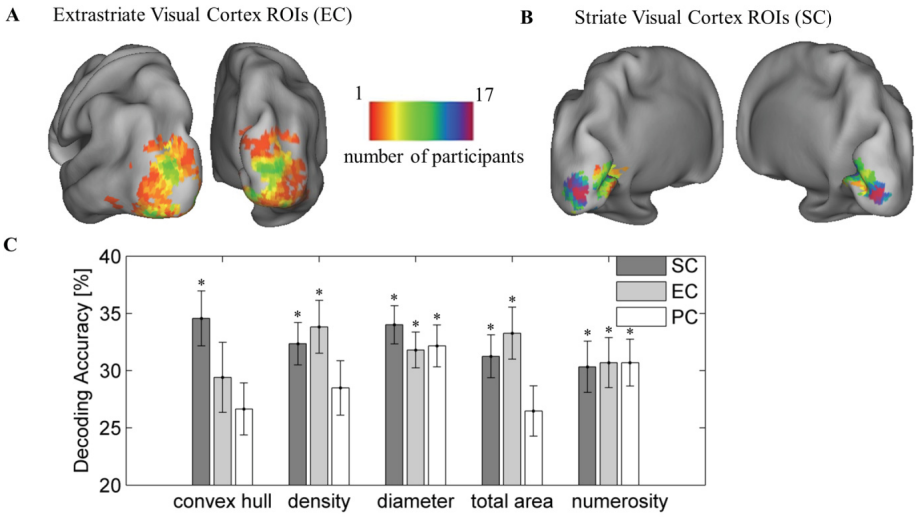

A
Extrastriate Visual Cortex ROIs (EC)
1
17
number of participants
B
Striate Visual Cortex ROIs (SC)
C
Decoding Accuracy [%]
40
35
30
25
20
SC
EC
PC
convex hull
density
diameter
total area
numerosity

Figure 4

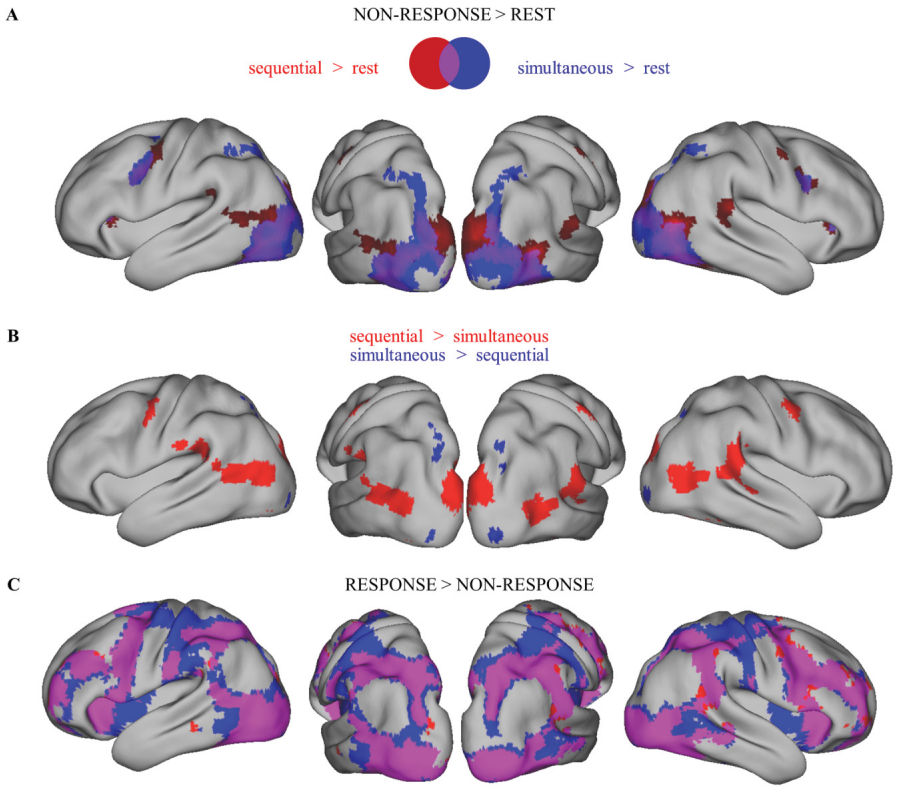

A
NON-RESPONSE > REST
sequential > rest
simultaneous > rest
B
sequential > simultaneous
simultaneous > sequential
C
RESPONSE > NON-RESPONSE

Figure 5

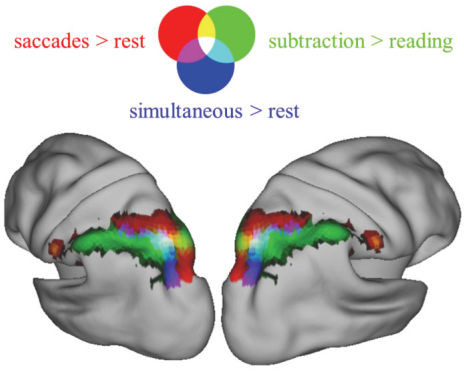
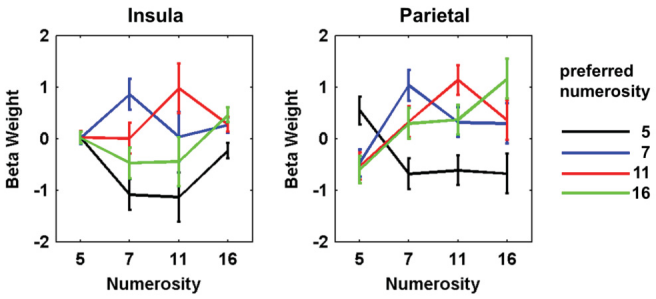


Figure 6


Insula
Parietal
Beta Weight
Numerosity
preferred numerosity
5
7
11
16

Tables

Table 1

	Peak Coordinates (MNI)					
	x	y	z	Peak z-score	Cluster Size	Label
simultaneous > rest	-8	-97	-10	9.09	2526	Area 18
	-36	-87	-10	9.07		L inferior occipital gyrus
	-18	-97	+3	8.66		L Area 18
	-43	-65	-3	7.72		L. Middle Temporal Gyrus
	-43	+1	-33	7.41	172	L. Precentral Gyrus
	-31	-47	+40	6.74	233	L. Inferior Parietal Lobule
	-23	-57	-48	5.72		L. Superior Parietal Lobule
	+30	-55	+50	6.24	98	R. Inferior Parietal Lobule
	+30	-85	-15	8.67	2375	R. Inferior Occipital Gyrus
	+40	-90	+15	7.68		R. Middle Occipital Gyrus
	+27	-95	+13	7.61		R. Superior Occipital Gyrus
	+37	-60	-13	7.43		R. Fusiform Gyrus
	-43	+1	+33	7.41	172	L. Precentral Gyrus
	+47	+1	+28	5.79	148	R. Precentral Gyrus
	+45	+8	+25	4.98		R. Inferior Frontal Gyrus
	+10	+16	+45	4.65	29	R. Middle Cingulate Cortex
	-31	-2	+50	3.90	21	L. Middle Fontal Gyrus
	-23	-5	+53	3.76		L. Superior Frontal Gyrus
	-31	+23	+8	3.89	17	L. Insula Lobe
	+32	+28	+5	4.38	16	R. Insula Lobe
sequential > rest	-33	-57	-15	11.20	9852	L. Fusiform Gyrus
	-16	-72	+8	11.20		L. Area 17
	+17	-72	+3	10.65		R. Area 17
	-43	+1	+33	6.21	280	L. Precentral Gyrus
	+65	-35	+15	5.21	160	R. Superior Temporal Gyrus
	+45	+8	+23	4.99	135	R. Area 44
	+47	+3	+28	4.83		R. Precentral Gyrus
	-33	+21	+8	6.46	75	L. Insula Lobe
	+40	+23	+3	4.85	75	R. Insula Lobe
	-46	-37	+25	5.23	42	L. Supramarginal Gyrus
	+55	-2	+50	5.03	41	R. Precentral Gyrus
	+52	-5	+53	4.86		R. Middle Frontal Gyrus

Table 2

Contrast	Peak Coordinates (MNI) x	y	z	Peak z-score	Cluster size	Label
simultaneous > rest and sequential > rest	-33	-57	-15	11.20	994	L. Fusiform Gyrus
	-11	-97	-8	8.91		L. Calcarine Gyrus
	-18	-90	-8	8.33		L. Middle Occipital Gyrus
	+32	-80	-13	9.04	782	R. Inferior Occipital Gyrus
	+45	-67	+8	8.74		R. Middle Temporal Gyrus
	+30	-72	-13	8.15		R. Fusiform Gyrus
	+22	-67	-10	7.89		R. Lingual Gyrus
	-43	+1	+33	6.21	71	L. Precentral Gyrus
	+25	-72	+25	6.58	68	R. Superior Occipital Gyrus
	+30	-80	+20	5.51		R. Middle Occipital Gyrus
	-13	-75	+10	9.98	50	L. Calcarine Gyrus
	+45	+8	+23	4.99	36	R. Inferior Frontal Gyrus
	+47	+3	+28	4.83		R. Precentral Gyrus
	+12	-72	+13	7.79	36	R. Calcarine Gyrus

Table 3

Contrast	Peak Coordinates (MNI) x	y	z	Peak z-score	Cluster size	Label
simultaneous > sequential	+34	-92	+1	7.19	56	R. V3v
	-31	-95	-5	6.33	37	L. V3v
	-21	-65	+48	5.56	30	L. Superior Parietal Lobule
	+32	-67	+33	5.54	20	R. Middle Occipital Gyrus
	+25	-62	+45	6.34	19	R. hIP3
sequential > simultaneous	-3	-85	+23	13.24	8822	L. Area 18
	-41	-72	+10	10.92		L. Middle Occipital Gyrus
	-21	-25	+48	4.16	145	L. Area 4p
	+47	+1	+48	6.31	99	R. Precentral Gyrus
	+17	-25	+45	5.86	79	R. Middle Cingulate Cortex
	-41	-7	+50	4.87	78	L. Precentral Gyrus
	-38	-7	-13	4.93	43	L. Insula
	+2	-25	+50	3.58	18	R. Middle Cingulate Cortex
	+7	-27	+53	3.47		R. SMA

954 **Table 4**

	Simultaneous (parietal)						Sequential (insula)					
	5 vs. 7		7 vs. 11		11 vs. 16		5 vs. 7		7 vs. 11		11 vs. 16	
	t(15)	p	t(15)	p	t(15)	p	t(15)	p	t(15)	p	t(15)	p
5	**9.77**	**< .001**	-0.85	.412	0.51	.618	**14.28**	**<.001**	0.31	.76	**-7.86**	**<.001**
7	**-13.94**	**<.001**	**12.42**	**<.001**	0.32	.76	**-17.20**	**<.001**	**19.30**	**<.001**	**-4.26**	**<.001**
11	**-7.43**	**<.001**	**-16.16**	**<.001**	**13.32**	**<.001**	0.25	.80	**-11.79**	**<.001**	**14.36**	**<.001**
16	**-4.22**	**<.001**	-1.23	.24	**-12.84**	**<.001**	**6.81**	**<.001**	-0.37	.72	**-22.19**	**<.001**

955

Die Selbständigkeitserklärung

Hiermit erkläre ich, dass ich die Dissertation selbständig und nur unter Verwendung der angegebenen Hilfen und Hilfsmittel angefertigt habe.

Datum Unterschrift

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Statement of Authorship

I hereby certify that this dissertation has been composed by me and is based on my own work, unless stated otherwise. Ideas and thoughts cited directly or indirectly from other work have been cited accordingly.

Date

Signature

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